

Management of Chronic Hepatitis B

Thomas B. Hargrave M.D

January 21, 2011

**CONTRA COSTA REGIONAL
MEDICAL CENTER
NOON CONFERENCE SERIES**

***DISCLOSURE OF CONFLICT OF
INTEREST***

- **Speaker has nothing to disclose**

Except for a short stint in juvie. Youthful indiscretion



Chronic Hepatitis B: Epidemiology

- 9th leading cause of mortality worldwide.
- >2 billion have been infected
 - 4 million acute cases per year
 - 1 million deaths per year
- Estimated 350 million chronic hepatitis B carriers world wide.
- In Asia, and most of Africa, chronic HBV affect 5-20% of the population
- 20-40% of chronic HBV will progress to cirrhosis or HCC



Chronic Hepatitis B Epidemiology

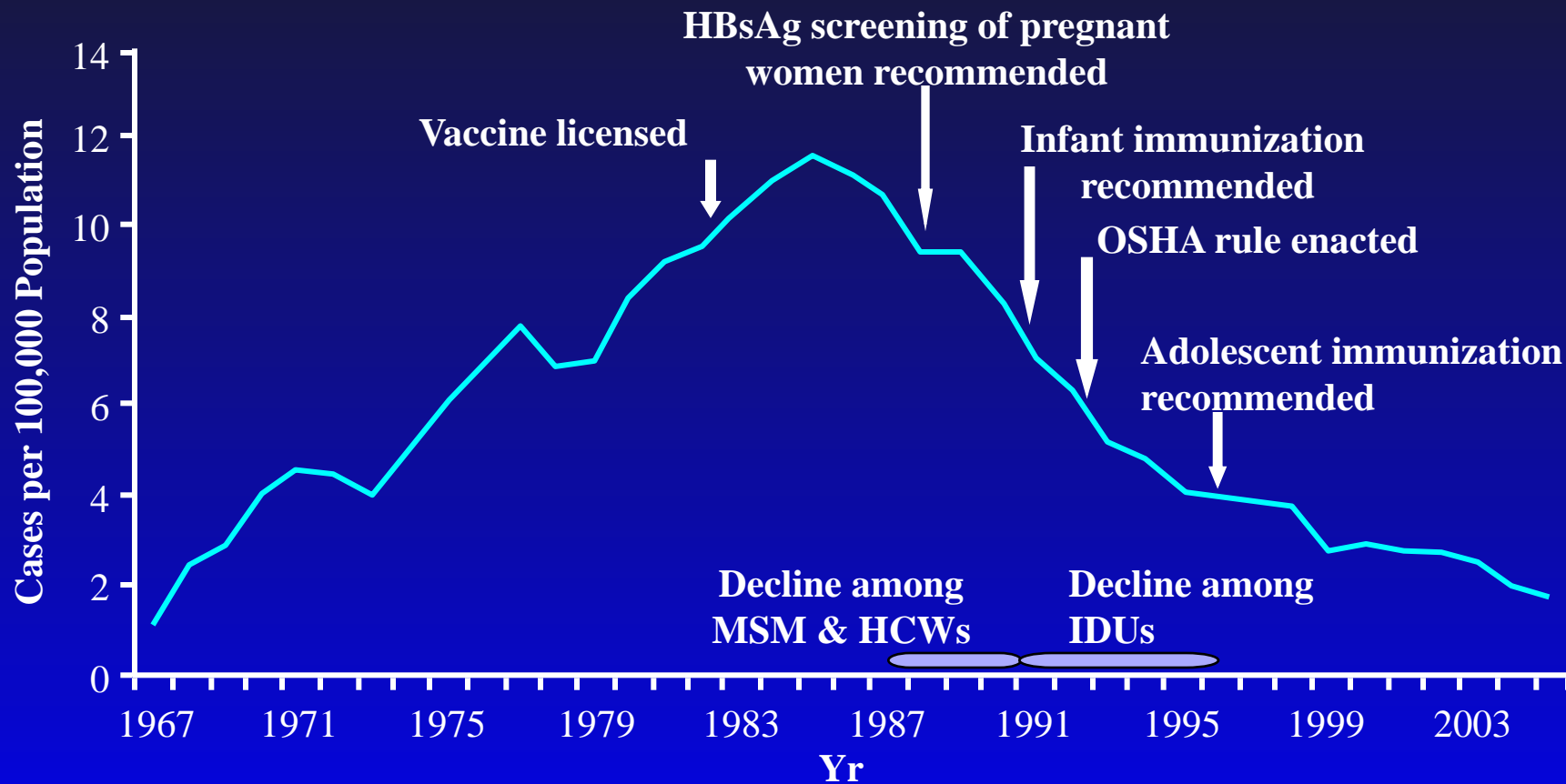
- In Western countries HBV is uncommon, affecting 0.2-1.0% of the general population
- Approx. 1.2 million chronic HBV carriers in the US, with an estimated 11,000 to 17,000 hospitalizations/year, and 4,000 to 5,500 deaths/year.
- In the US, ~70% of chronic HBV infections are acquired in adulthood, 30% perinatally acquired, mostly in Asian immigrant populations.



Acute Hepatitis B

- **In the US, the incidence of acute HBV has declined 70% in the last 2 decades**
- **Decrease evident in all age, racial/ethnic, and high-risk groups, but greatest in groups with the highest vaccination rates (children and health care workers).**
- **Vaccination, and a decline in intravenous drug, use accounts for the majority of the decline in acute HBV**

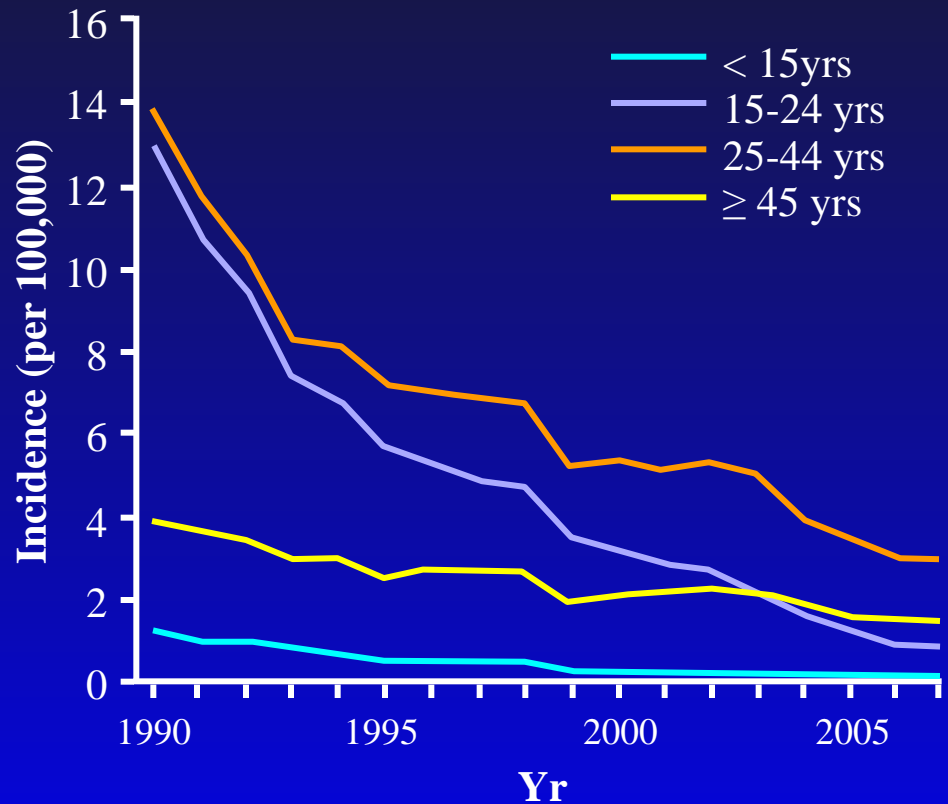
HBV Incidence by Year: United States (1966-2005)



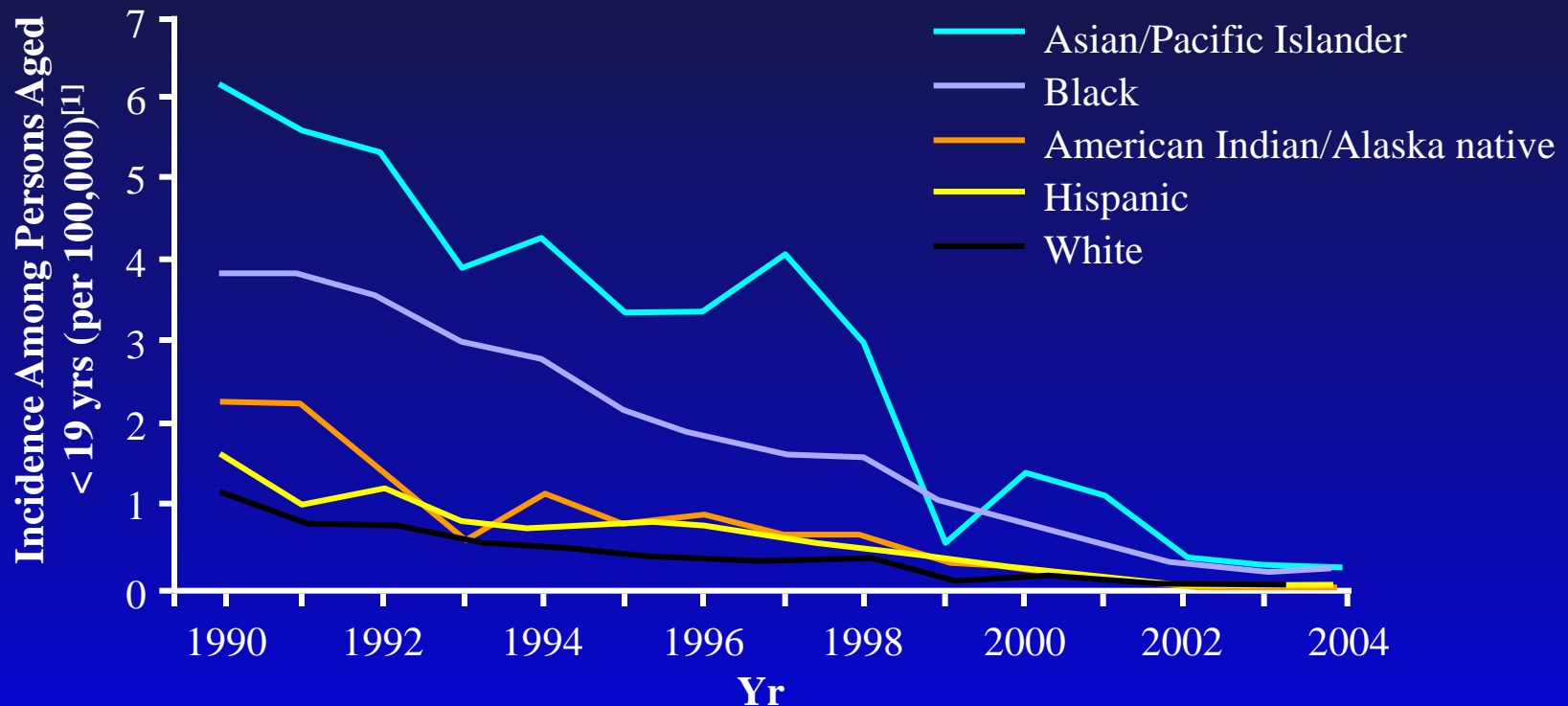
Wasley A, et al. MMWR Surveill Summ. 2008;57(2):1-24. Wasley A, et al. MMWR Surveill Summ. 2007;56(3):1-24. OSHA. Available at: http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10051.

Reduced Incidence of HBV Infection in US

- **Incidence of acute HBV infection reduced 82% from 1990 to 2007**
 - 2007: 43,000 new infections
 - Largest % declines were among younger populations
 - More effective strategies needed for adult population
- Estimates limited by underreporting because acute infection is frequently asymptomatic or resembles other illnesses



Reduced Incidence of HBV Infection Among Children of All Races in the US



- Despite dramatic reduction in childhood infection rates, ~ 1000 cases of perinatal HBV infection are estimated to occur each yr^[2]

1. Mast EE, et al. MMWR Recomm Rep. 2005;54(RR-16):1-31.

2. Ward JW. Am J Public Health. 2008;98:779-781.

Which of the following groups has the highest risk of chronic HBV infection?

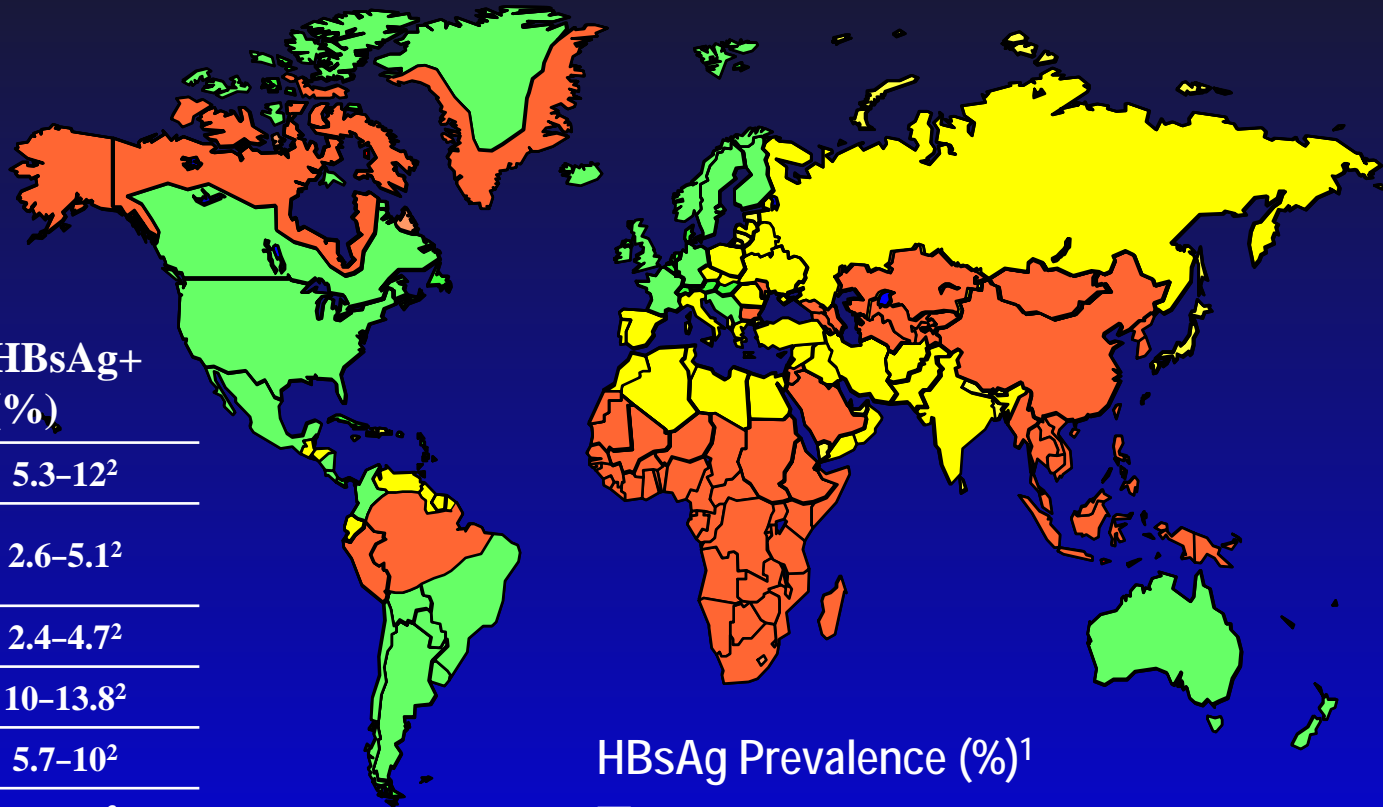
- A) The child of an Asian immigrant**
- B) A person who has recently moved from South Africa**
- C) A US-born healthcare worker**
- D) US born dialysis patient**

Which of the following groups has the highest risk of chronic HBV infection?

- A) The child of an Asian immigrant
- B) **A person who has recently moved from South Africa**
- C) A US-born healthcare worker
- D) US born dialysis patient

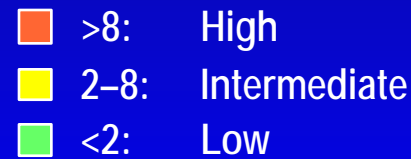
HBV

A Global Health Problem



Country	HBsAg+ (%)
China	5.3–12 ²
South Korea	2.6–5.1 ²
India	2.4–4.7 ²
Taiwan	10–13.8 ²
Viet Nam	5.7–10 ²
Japan	4.4–13 ³
Africa	5–19 ²
Russia	1.4–8 ²
Europe	0.3–12 ²

HBsAg Prevalence (%)¹



1. WHO. Hepatitis B. 2002. 2. Custer B. et al. *J Clin Gastroenterol*. 2004;38(10 suppl):S158. 3. WHO/WPRO data.

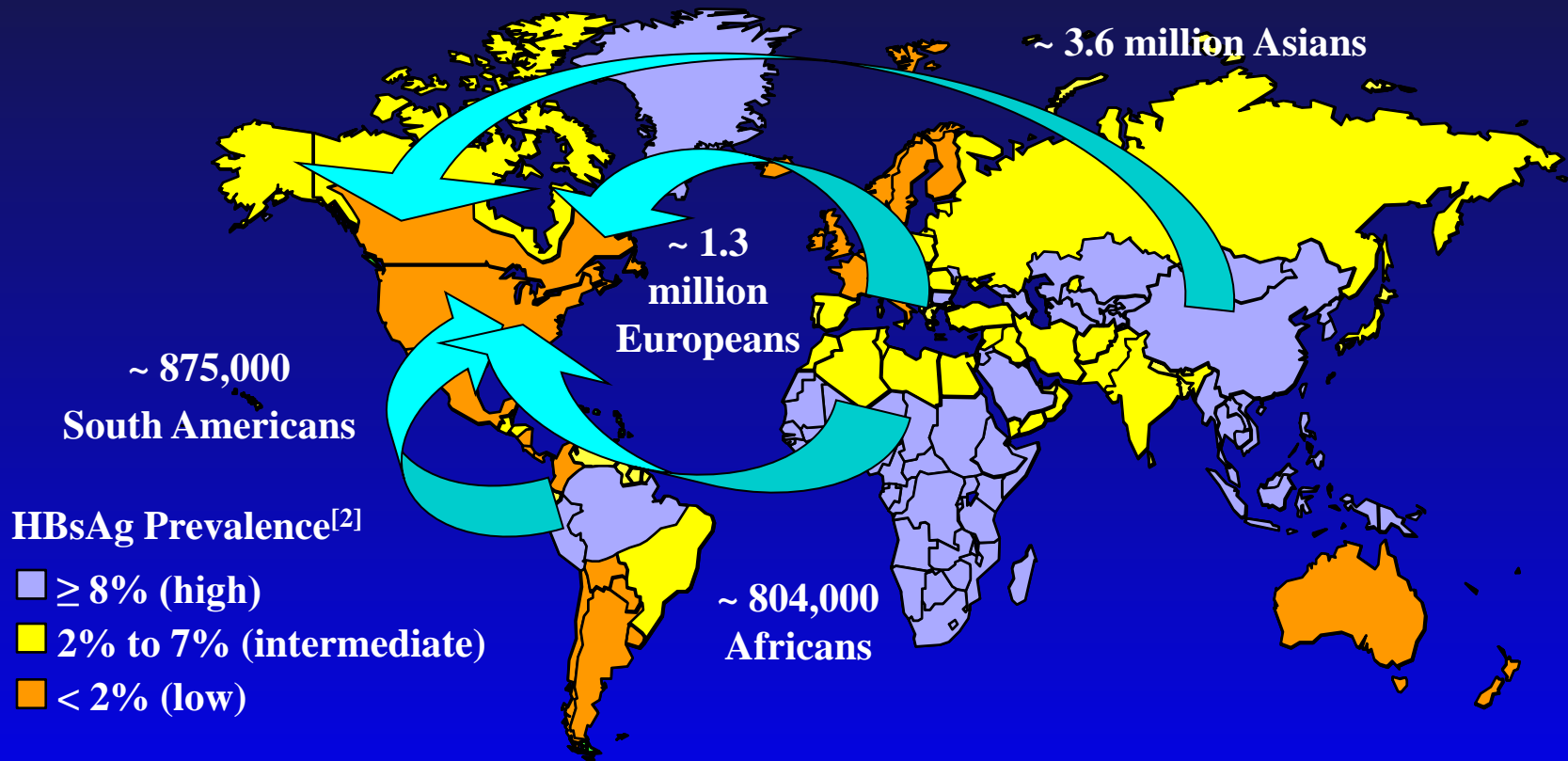
Estimated Prevalence of HBsAg-Positive Persons in the US by Population Segment

Population Group	CHB Prevalence, % ^[1,2]
US-born API	1.40
Foreign-born API	8.90
Non-Asian Americans	0.42
Correctional institutions	2.00
Other group living quarters	0.50

- Age-adjusted prevalence of anti-HBc and HBsAg in the US statistically similar during 1999-2006 vs 1988-1994^[3]
- ~ 40,000 persons with chronic HBV infection immigrate to US each yr^[4]

Impact of Immigration on US HBV Prevalence

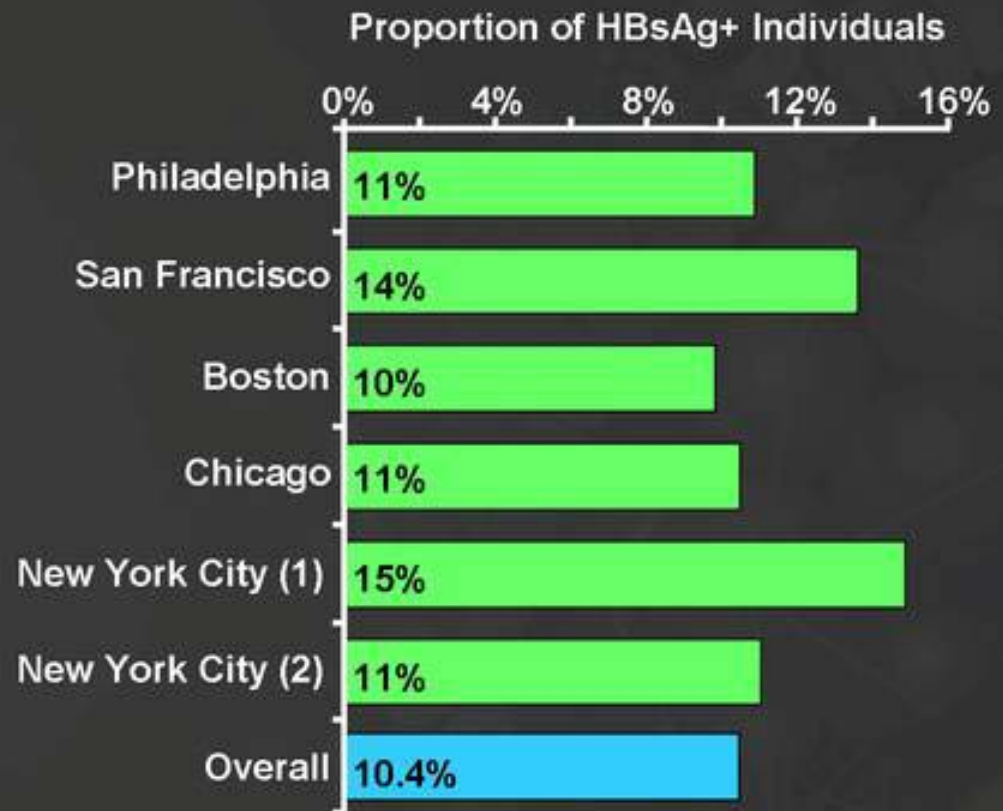
Immigration Numbers by Continent: 2000-2009^[1]



1. US Department of Homeland Security. Yearbook of Immigration Statistics: 2009. 2. Weinbaum CM, et al. MMWR Recomm Rep. 2008;57(RR-8):1-20.

HBV Seroprevalence Among Asian Americans

- 5 large US cities (2001-2004)
 - Chinese
 - Korean
 - Vietnamese
- Median age
 - 43 yr (12-80)
- HBsAg+, overall
 - 558/5341 (10.4%)



Transmission

Hepatitis B: Transmission

- **Highly infectious, high concentrations in blood, semen and serous fluids**
- **Infectious virions stable on environmental surfaces for up to seven days.**
- **Four major modes of transmission**
 - **Vertical (perinatal)**
 - **Percutaneous/parenteral**
 - **Sexual**
 - **Horizontal (personal contact)**

Transmission Routes and Endemicity

- **Most primary HBV infections in highly endemic countries occur during infancy or early childhood^[1]**
 - Vertical transmission (from infected mother via perinatal exposure) or horizontal transmission
 - Involves highest chronic infection risk
- **Most primary HBV infections in low prevalence countries occur during adolescence/young adulthood^[1]**
 - Transmission routes: unsafe sex practices or injection drug use
- **~ 21 million HBV infections worldwide in 2000 attributable to unsafe injection administration in healthcare settings^[2]**

Risk Factors Associated With HBV in the United States: 2007

Risk Factor	Cases,* %
Multiple sex partners	38.3
Injection drug use	15.0
Surgery	11.7
Men who have sex with men	10.5
Sexual contact with hepatitis B patient	6.2
Percutaneous injury	4.3
Household contact of hepatitis B patient	2.3
Medical employee with blood contact	0.6
Blood transfusion	0.5
Hemodialysis	0.2
Unknown	58.0

*Percentage of cases calculated based on total number of cases for which any data for that exposure type were reported. Percentages do not total 100% because multiple risk factors could be reported by a single case.

Screening and Vaccination for HBV

Which of the following is NOT listed as a group for whom HBV screening is recommended?

- A) All women of childbearing age**
- B) Persons needing immunosuppressive therapy**
- C) Men who have sex with men**
- D) Persons born in Asia**
- E) HCV-infected individuals**



Who Should Be Screened?

- **Patients with abnormal ALT**
- **Patients engaged in high-risk sexual behaviors**
- **Injection drug users**
- **Immigrants, refugees, or adoptees from areas of high endemicity**
- **Immunocompromised patients**
- **Dialysis patients**
- **Recipients of organ/tissue transplants or blood transfusion**
- **Household members or sexual partners of known HBV carriers**
- **Occupational exposure (healthcare workers, police, EMTs)**
- **Inmates in long-term correctional facilities or residents in institutions for the developmentally disabled**
- **Pregnant women**
- **Individuals infected with HCV or HIV**

Adapted from CDC. *Epidemiology & Prevention of Vaccine-Preventable Diseases*. "The Pink Book." 8th ed, 2005.
Lok ASF, et al. *Hepatology*. 2001;34:1225.

AASLD Guideline Recommendations for HBV Screening

"1. The following groups should be tested for HBV infection (Grade I)"

- **Persons born in high* or intermediate† endemic areas**
 - Asia, Africa, and South Pacific Islands: all countries
 - Middle East (except Cyprus and Israel)
 - European Mediterranean: Malta and Spain
 - The Arctic (indigenous populations of Alaska, Canada, and Greenland)
 - South America: Ecuador, Guyana, Suriname, Venezuela, and Amazon regions of Bolivia, Brazil, Colombia, and Peru
 - Eastern Europe: all countries except Hungary
 - Caribbean: Antigua and Barbuda, Dominica, Granada, Haiti, Jamaica, St Kitts and Nevis, St Lucia, and Turks and Caicos
 - Central America: Guatemala and Honduras

In other words, test just about everyone at CCRMC!

HBV Vaccine: Indications

- **Routine vaccination of infants**
 - Regardless of mother's HBsAg status
 - With HBIG for HBsAg positive mothers
- **Catch-up vaccination of children and adolescents**
- **Vaccination of adults with risk factors for infection**
 - High-risk sexual activity
 - Illegal injection drug use
 - Occupational exposure
 - Hemodialysis patients
 - Household contacts of infected persons



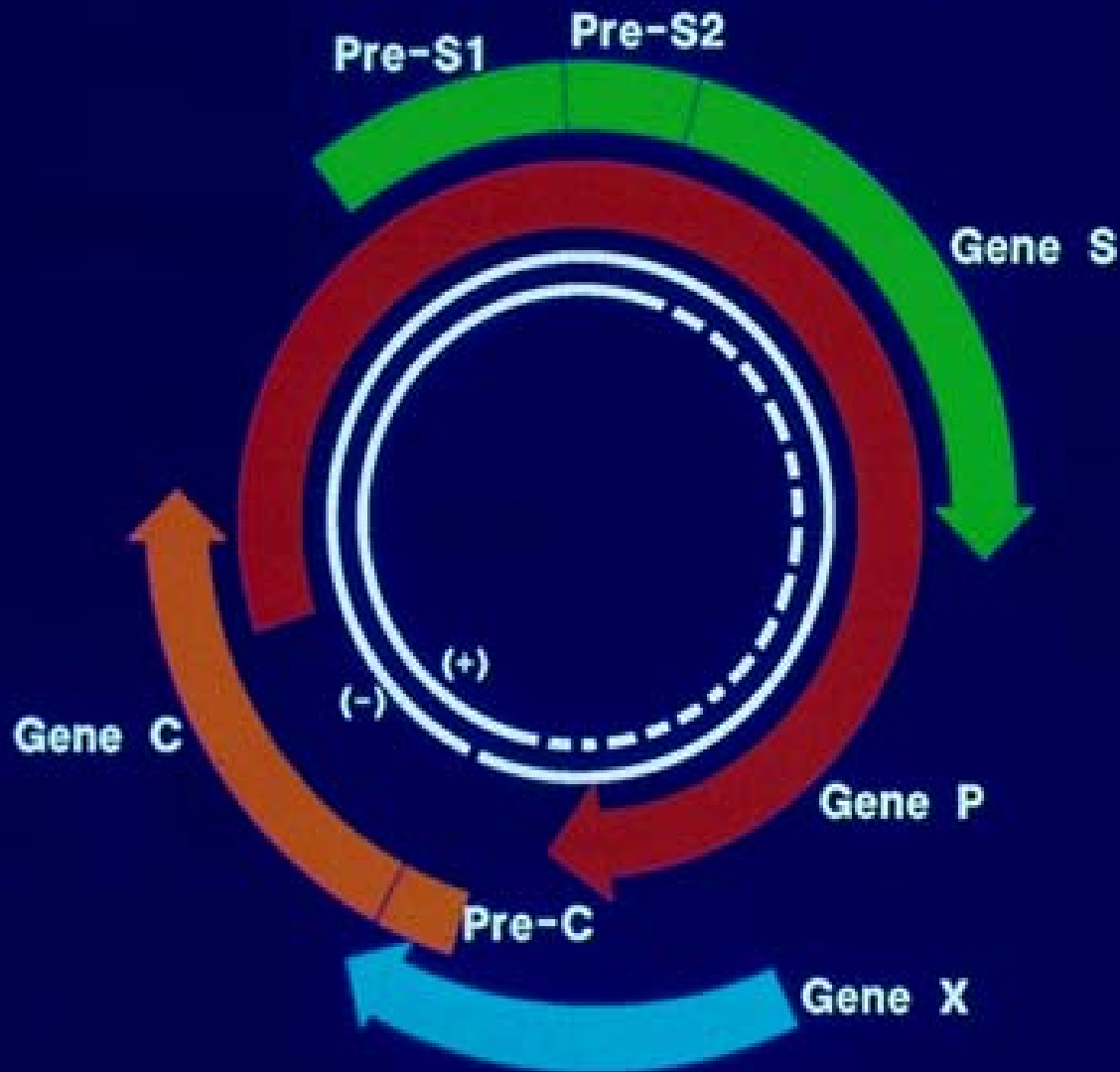
Prevention of HBV Transmission

- Sexual contacts should be vaccinated
- Use barrier protection during sex
- Do not share razors or toothbrushes
- No blood, sperm donation
- Cover open cuts/scratches
- Permitted activities:
 - Participation in contact sports
 - Participation in daycare and school activities
 - Sharing food, utensils, kissing

Pathophysiology and Natural History

HBV

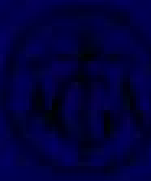
Genes and Gene Products

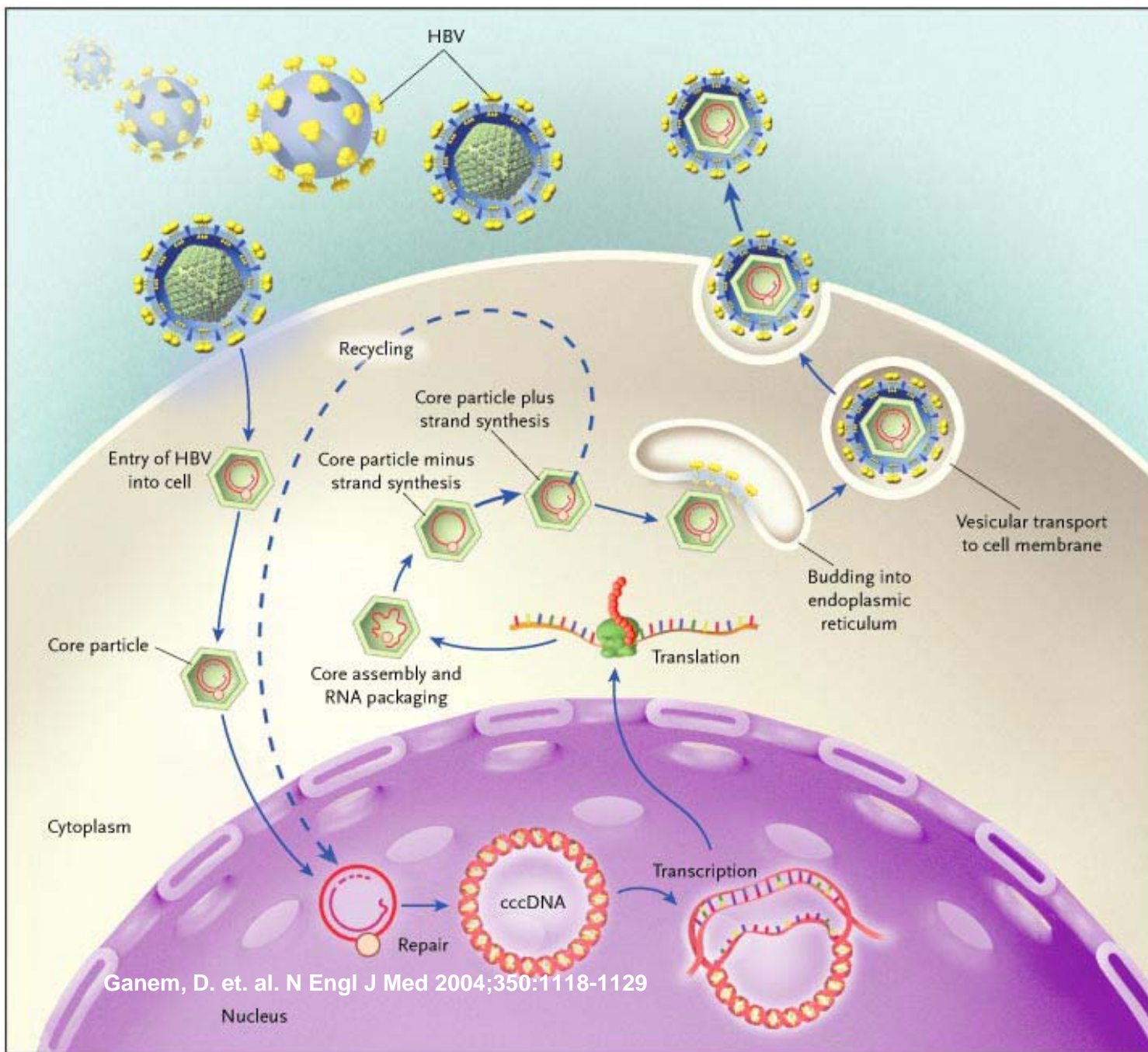


Circular, partially double-stranded DNA, 3200 base pairs

Products

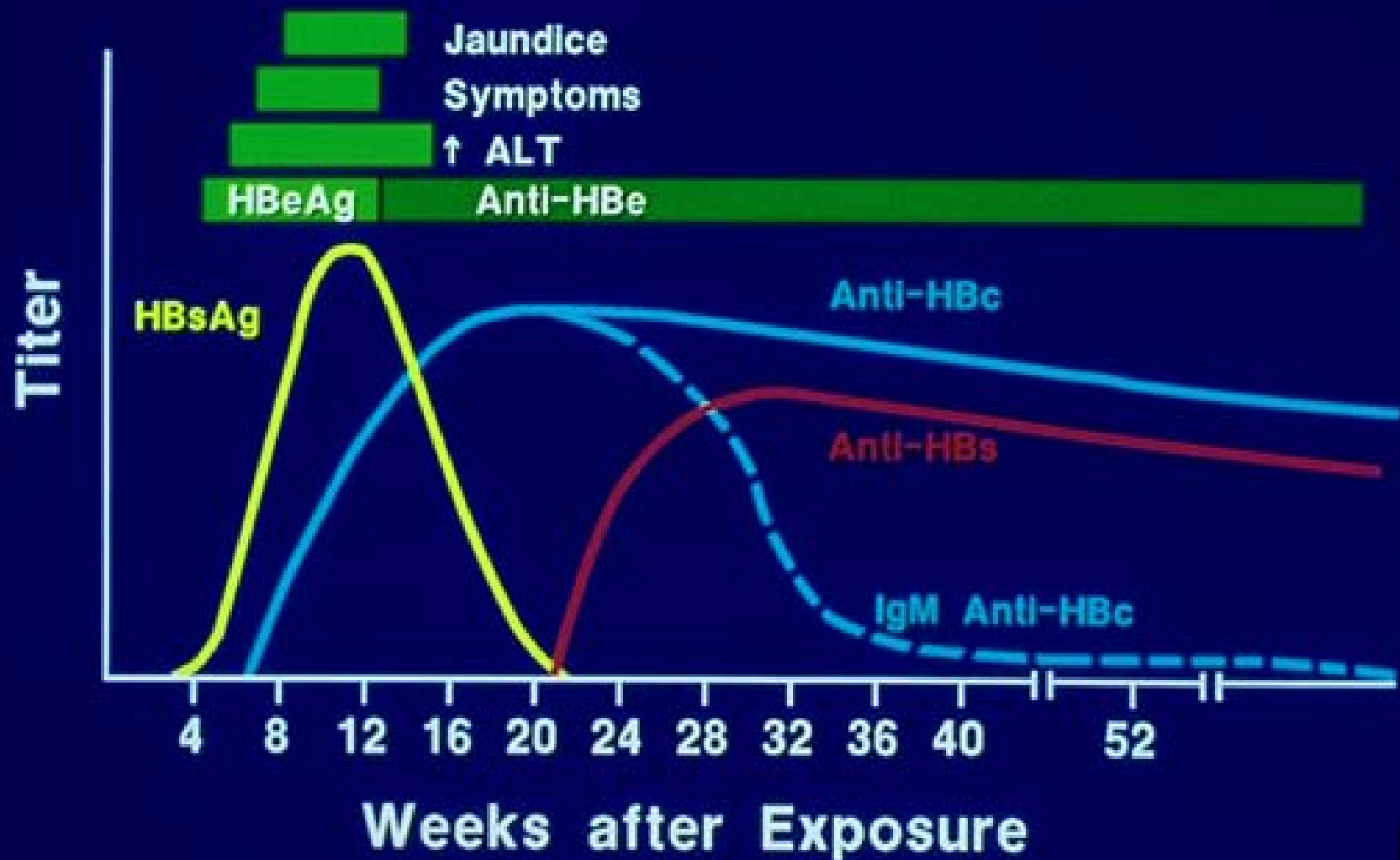
- HBsAg
- DNA Polymerase
- HBxAg
- HBcAg/HBeAg





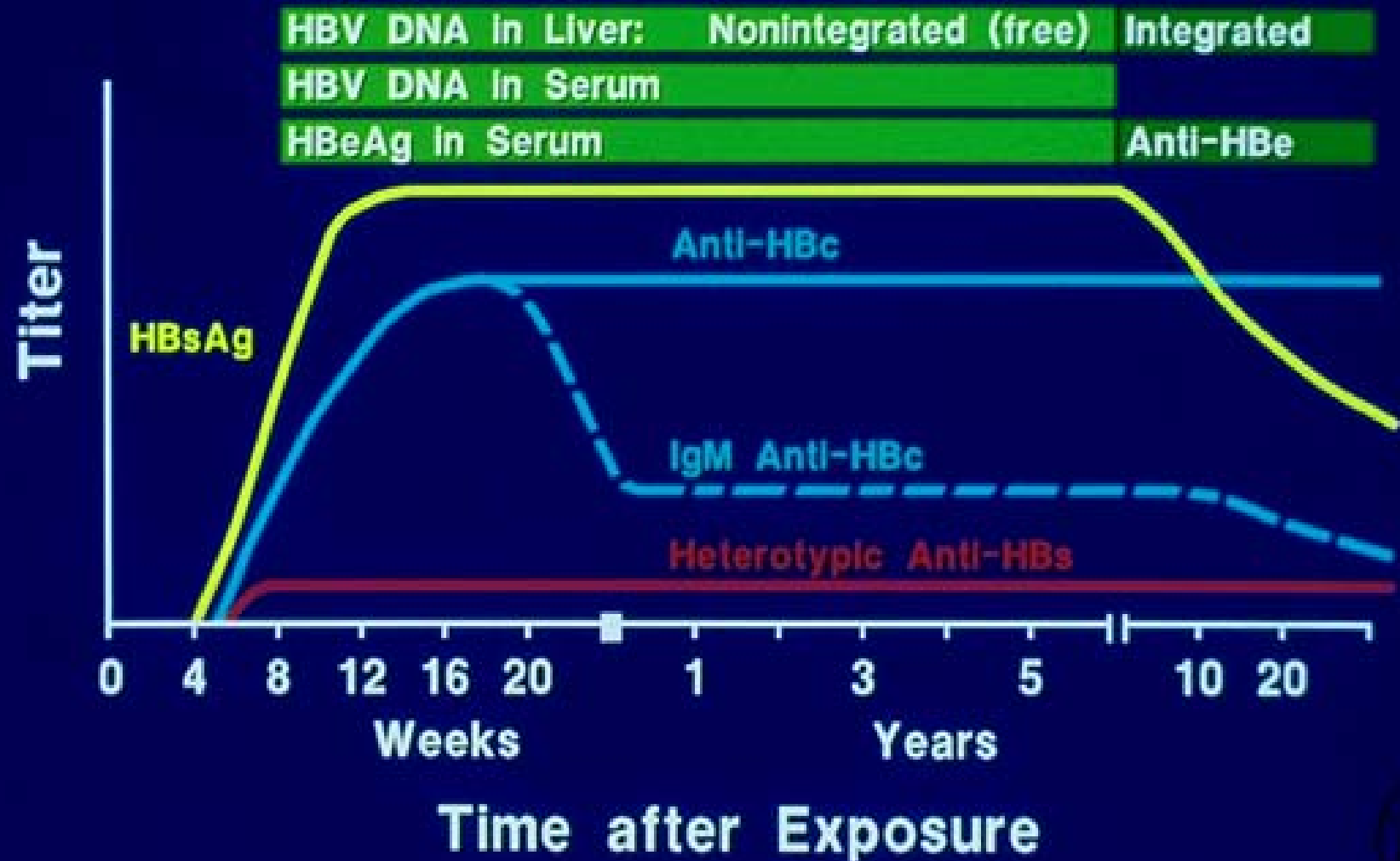
ACUTE HBV INFECTION

Sequence of Events



CHRONIC HBV INFECTION

Sequence of Events



Natural History of HBV

Fulminant Hepatitis <1%

Asymptomatic
Infection 65%

Recovery
Immunity

Clinical Acute
Hepatitis 35%

Risk of chronic
HBV varies with age

Chronic HBV <5%

15% females
40 % males

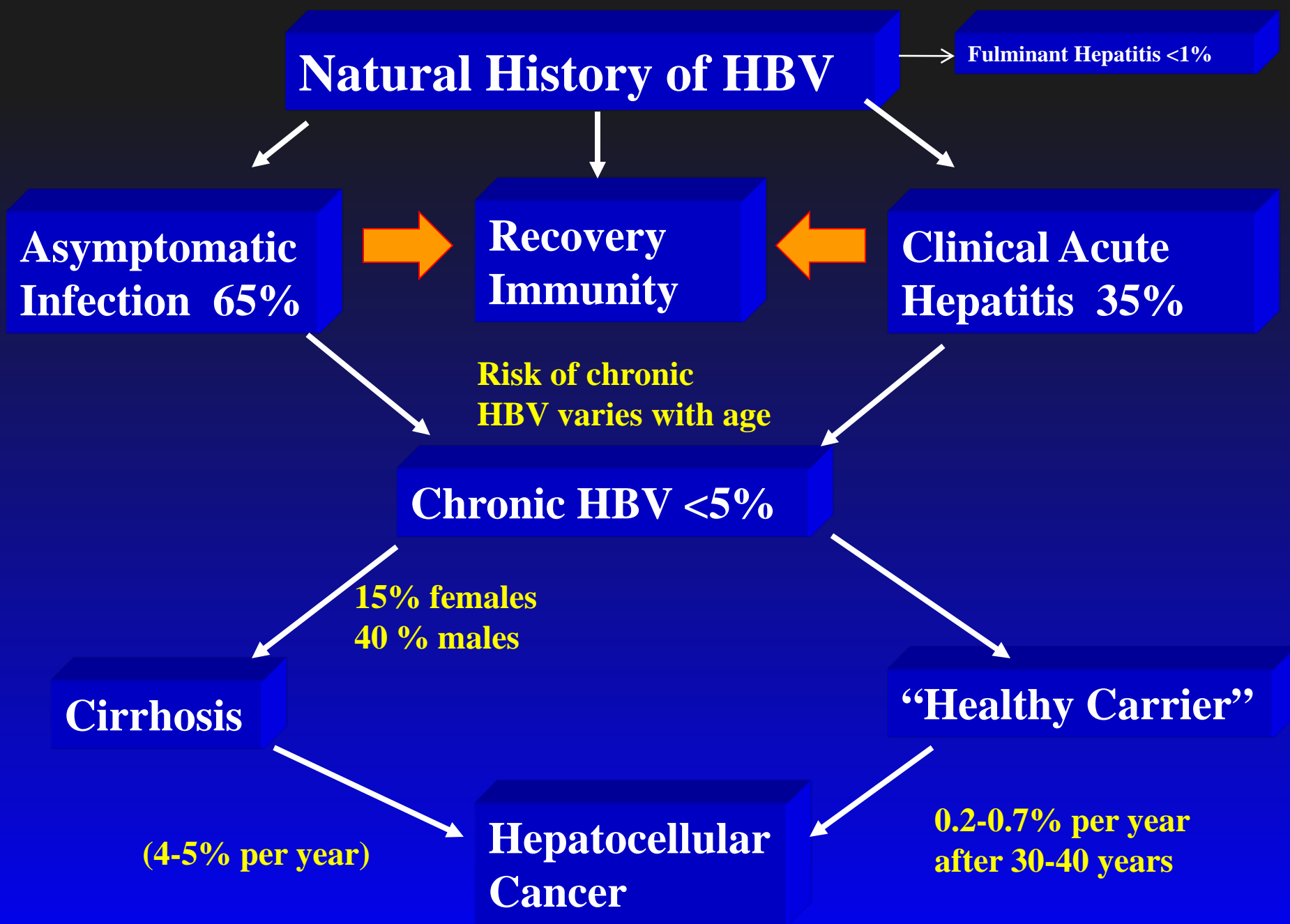
Cirrhosis

(4-5% per year)

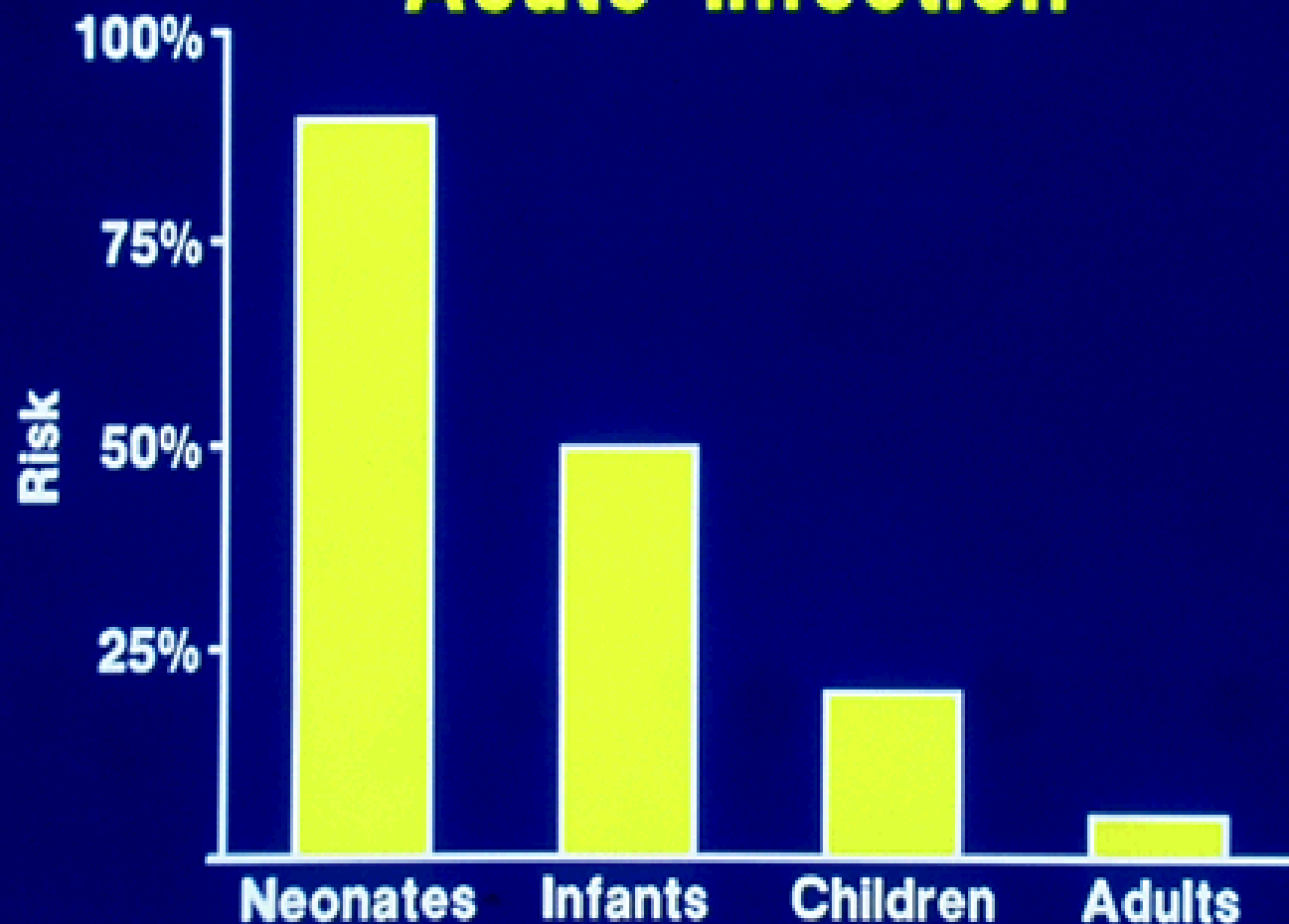
Hepatocellular
Cancer

“Healthy Carrier”

0.2-0.7% per year
after 30-40 years



Risk of Carrier State after Acute Infection





Risk Factors for Progression to Cirrhosis or HCC in HBsAg-Positive Individuals

- **Host**
 - Older age (> 40 yrs)
 - Male sex
 - Asian/African ancestry
 - HCC family history
- **Viral**
 - HBeAg positive
 - Higher HBV DNA
 - Genotype B, C
 - Precore mutation
 - Basal core promoter mutation
- **Clinical**
 - Cirrhosis
 - HCV coinfection
- **Other**
 - Smoking, alcohol
 - Obesity, diabetes

Initial Evaluation of Chronic HBV–Infected Patients

Initial Evaluation

History and physical examination

Family history of liver disease, HCC

Laboratory tests to assess liver disease: CBC with platelets, hepatic panel, and prothrombin time

Tests for HBV replication: HBeAg/anti-HBe, HBV DNA

Tests to rule out viral coinfections: anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV in those at risk

Tests to screen for HCC: AFP and ultrasound as appropriate

Consider liver biopsy to grade and stage liver disease: for patients who meet criteria for chronic hepatitis

Lok AS, McMahon BJ. Hepatology. 2009;50:661-662. Chronic Hepatitis B: Update 2009, Lok ASF, McMahon BJ, www.aasld.org. Copyright©2009. American Association for the Study of Liver Diseases, Reproduced with permission of the American Association for the Study of Liver Diseases.

Chronic HBV Infection: Diagnostic Criteria

Disease Phase	Diagnostic Criteria
Chronic hepatitis B	<ul style="list-style-type: none">▪ HBsAg+ > 6 mos▪ Serum HBV DNA > 20,000 IU/mL (10^5 copies/mL), lower values 2000-20,000 IU/mL (10^4-10^5 copies/mL) often seen in HBeAg- disease▪ Persistent or intermittent elevation in ALT/AST levels▪ Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation
Inactive HBsAg carrier state	<ul style="list-style-type: none">▪ HBsAg+ > 6 mos▪ HBeAg-, anti-HBe+▪ Serum HBV DNA < 2000 IU/mL▪ Persistently normal ALT/AST levels▪ Liver biopsy confirms absence of significant hepatitis
Resolved hepatitis B	<ul style="list-style-type: none">▪ Previous known history of acute or chronic hepatitis B or presence of anti-HBc +/- anti-HBs▪ HBsAg-▪ Undetectable serum HBV DNA (very low levels may be detectable by sensitive PCR assays)▪ Normal ALT levels

Lok AS, McMahon BJ. Hepatology. 2009;50:661-662. Chronic Hepatitis B: Update 2009, Lok ASF, McMahon BJ, www.aasld.org. Copyright@2009. American Association for the Study of Liver Diseases, Reproduced with permission of the American Association for the Study of Liver Diseases.

Chronic HBV: Phases of Infection

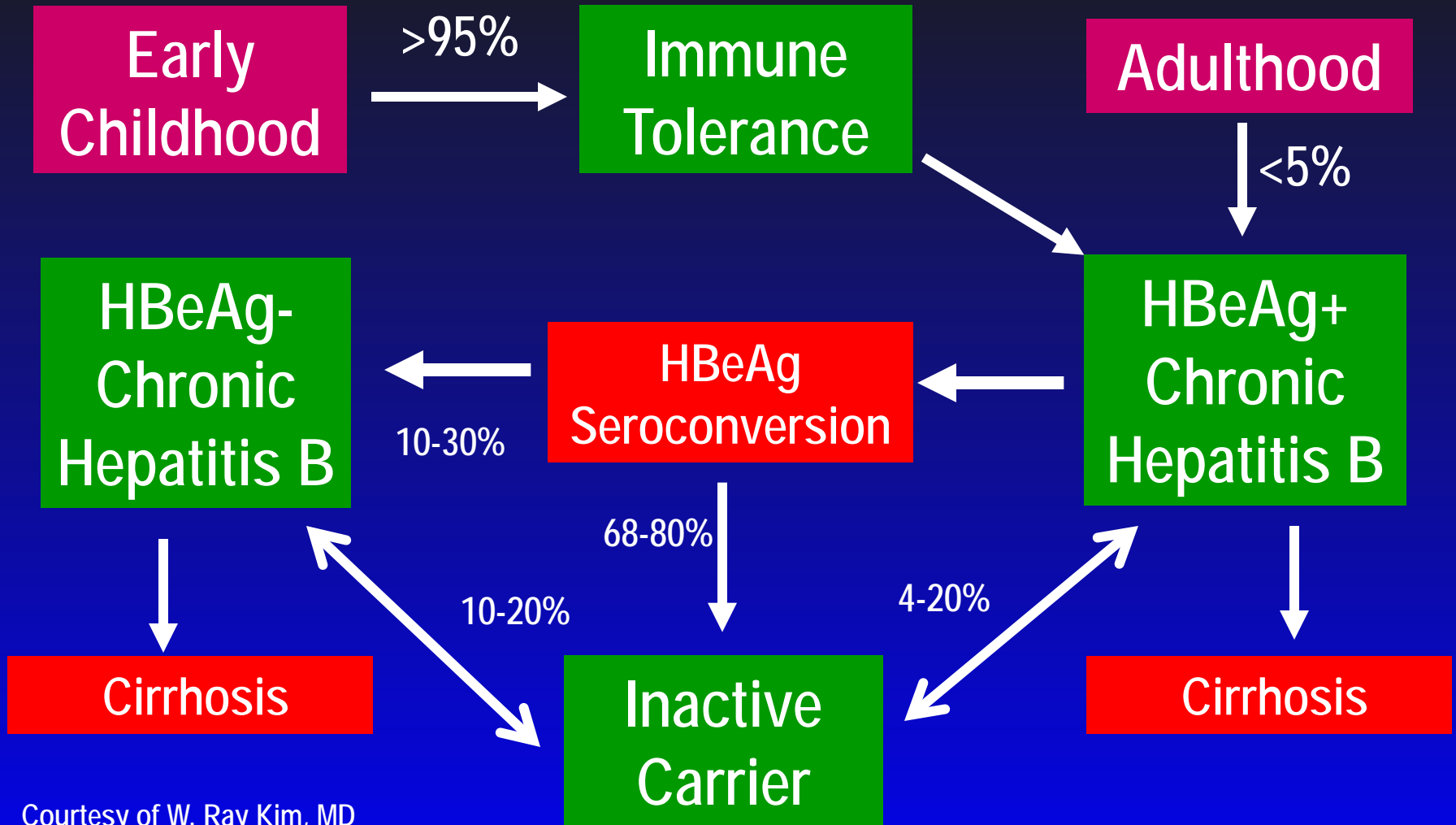
- **Replicative Phase**
 - **(I) Immune Tolerance**
 - **(II) Immune Clearance**
- **Nonreplicative (Low-Replicative) Phase (III)**
- **Immune Phase (IV)**

Phases of Chronic HBV Infection

	Immune Tolerance	Immune Active/ HBeAg-Positive CHB	Nonreplicative (Inactive Carrier)	HBeAg-Negative CHB
Typical HBV DNA, IU/mL	> 200,000 and often > 10^{7-8}	200,000 - 2×10^9	< 2000	2000 - 2×10^7
HBeAg	Positive	Positive	Negative	Negative
ALT	Normal	Elevated or fluctuating	Normal	Elevated or fluctuating
Other observations	Liver biopsy typically normal or minimal findings	Active inflammation on liver biopsy	HBsAg may become undetectable	Active inflammation on liver biopsy
Treatment candidate?	No	Yes	No	Yes

1IU = ~5 copies/mL

Natural History of Chronic HBV

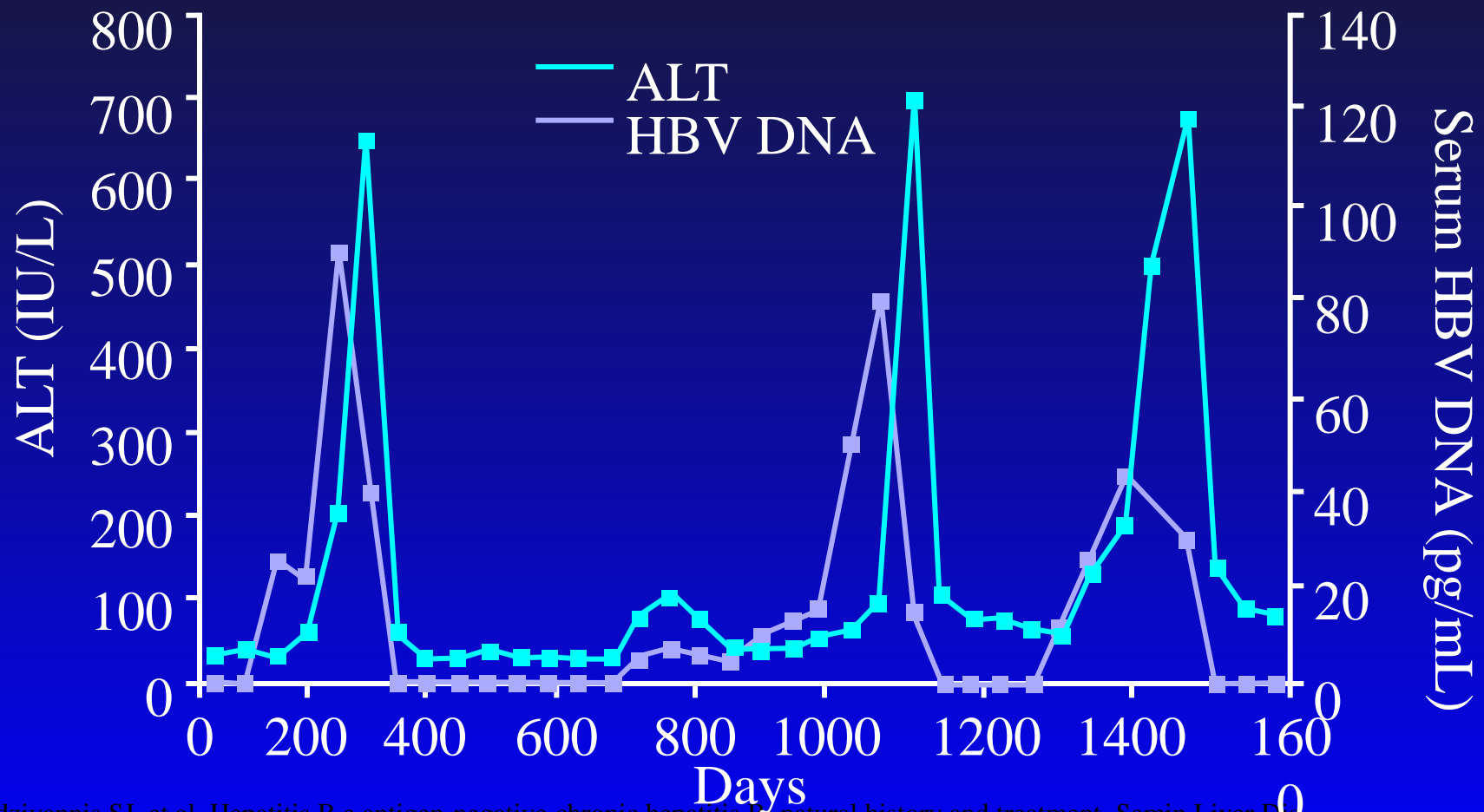


Courtesy of W. Ray Kim, MD

Chen DS, et al. *J. Gastroenterol Hep.* 1993;8(5):470.

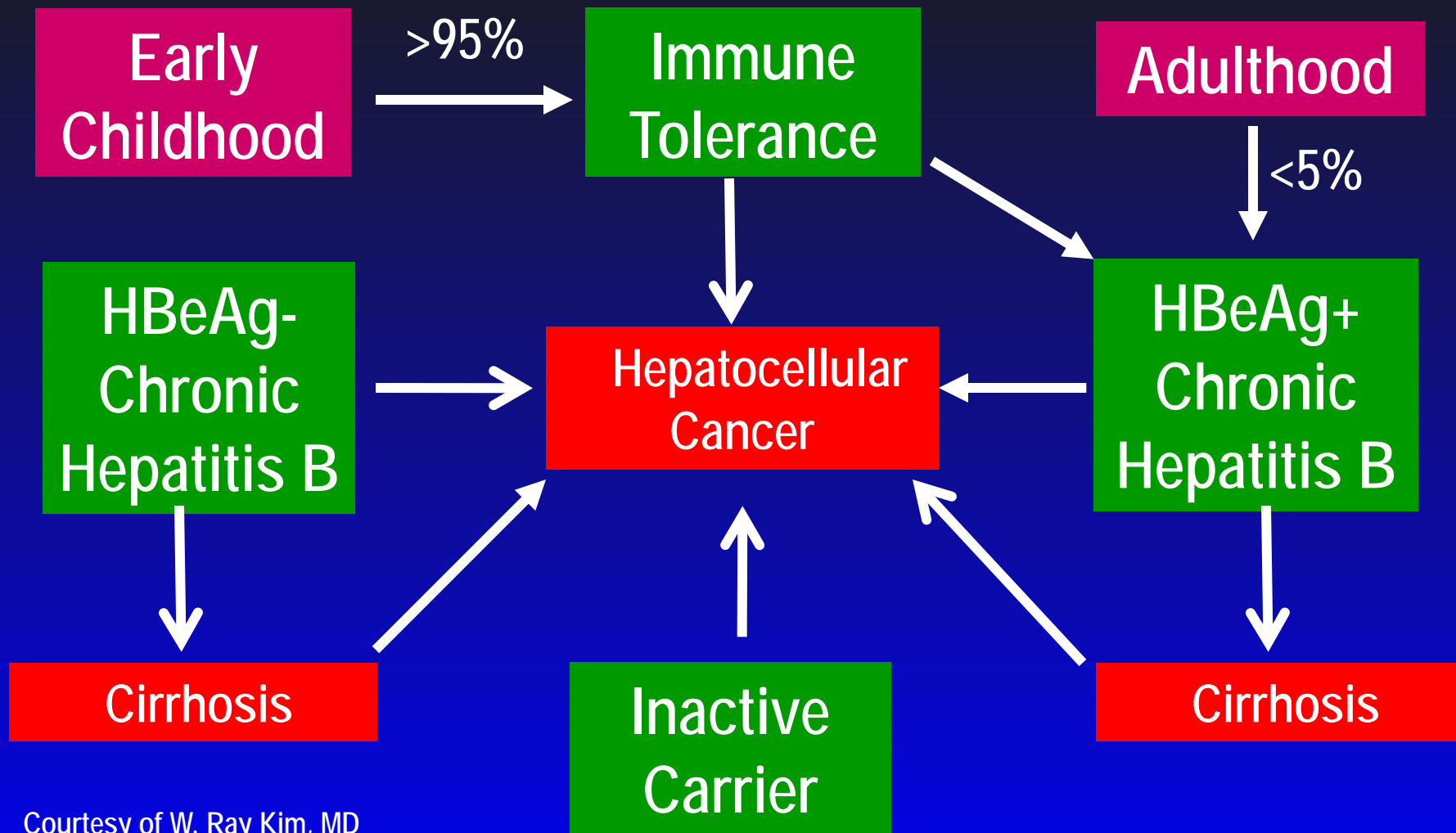
Seeff L, et al. *N Engl J Med.* 1987;316(16):965.

HBeAg-Negative Patients Require Frequent Monitoring



Hadziyannis SJ, et al. Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. *Semin Liver Dis.* 2006;26(2):130-141. Reprinted by permission.

HCC Risk of Chronic HBV



Courtesy of W. Ray Kim, MD

Chen DS, et al. *J. Gastroenterol Hep.* 1993;8(5):470.

Seeff L, et al. *N Engl J Med.* 1987;316(16):965.

Who Are Treatment Candidates?

Candidacy for Anti-HBV Treatment

In general, a patient with chronic HBV is a treatment candidate if there is evidence of:

- HBV replication (HBV DNA+)
- Liver disease (elevated ALT)
 - The true normal ALT:
 - Females: <19
 - Males: <30

HBV DNA and Prognosis

Immune-mediated injury appears to cease when HBV DNA < 10,000 copies/ml HBV viral load predicts

- Progression of liver disease¹
- Cirrhosis¹
- Cirrhosis-related complications²
- HCC^{1,3}
 - Independent of HBeAg, ALT, and cirrhosis³

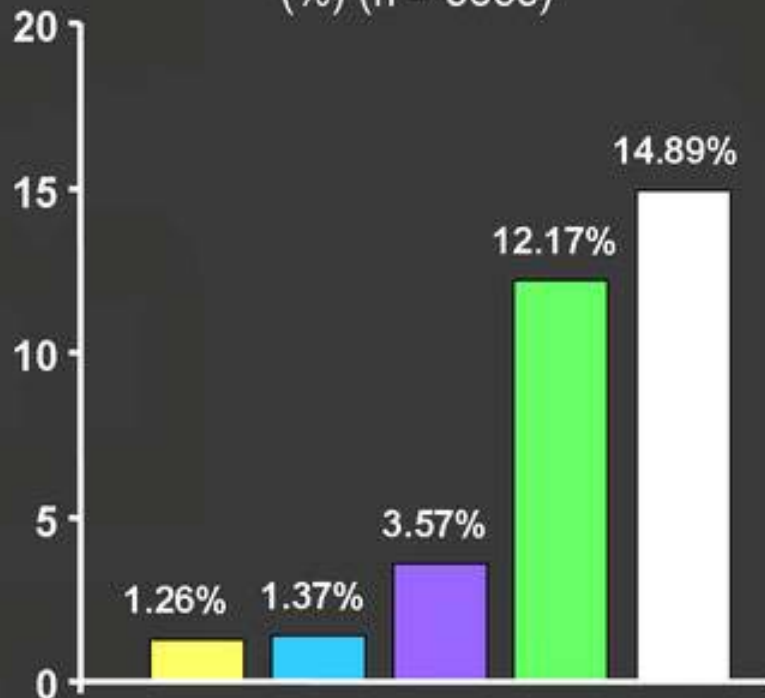
1. Chen G, et al. Abstract 996. Presented at: AASLD 2004. 2. Yuan JH, et al. *J Viral Hepat.* 2005;12:373.

3. Chen C-J, et al. *JAMA.* 2006;295:65.

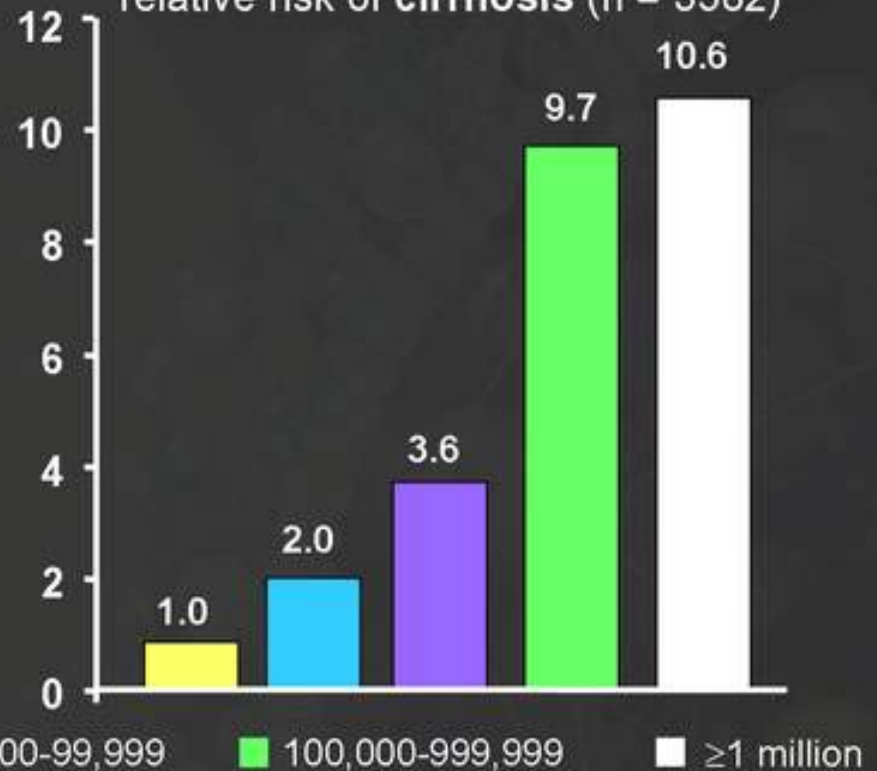
REVEAL Study: HBV DNA Levels and Long-term Outcomes

Viral Load at Baseline

Cumulative Incidence of HCC (%) (n = 3653)



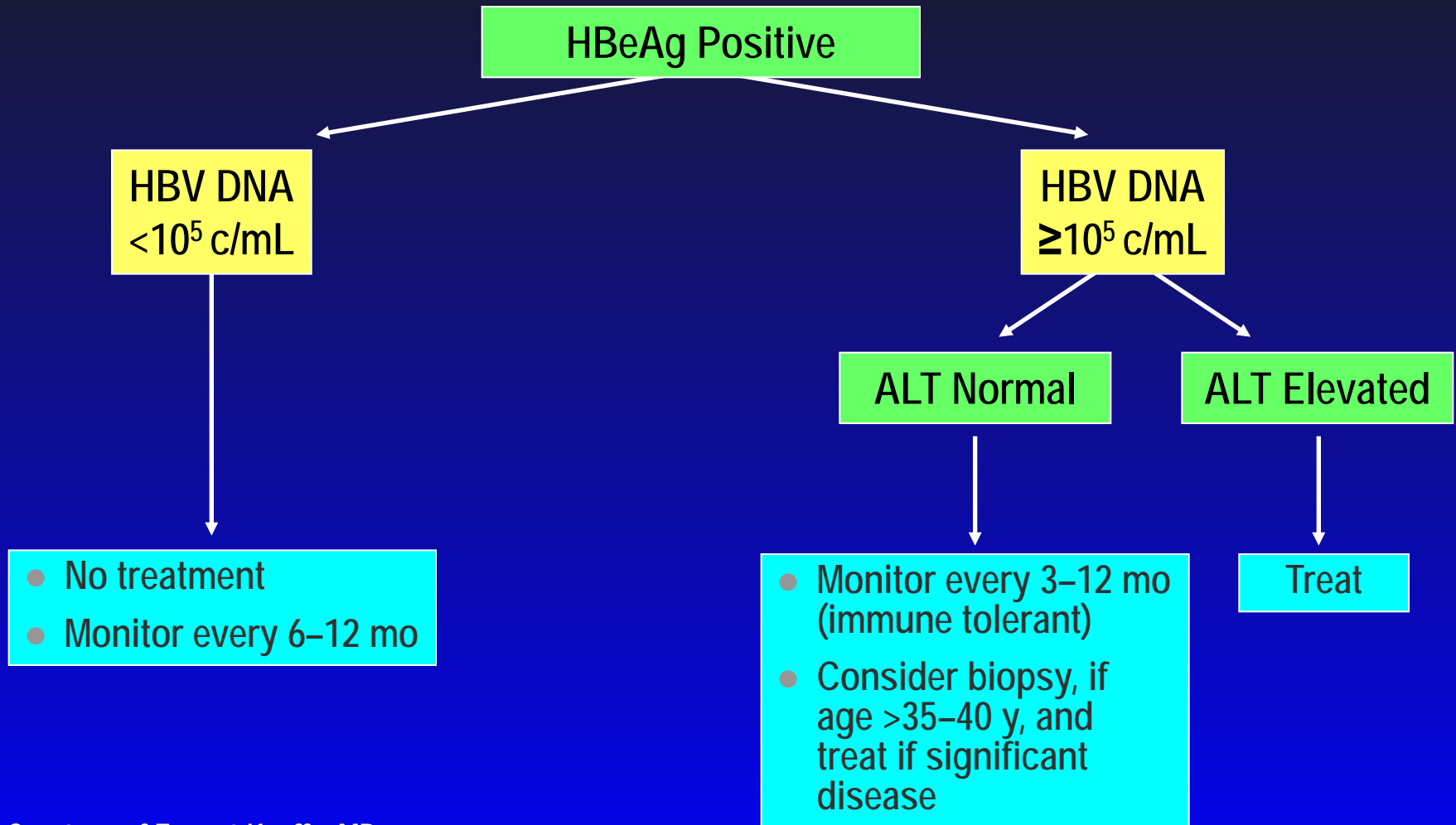
Multivariate-adjusted relative risk of cirrhosis (n = 3582)



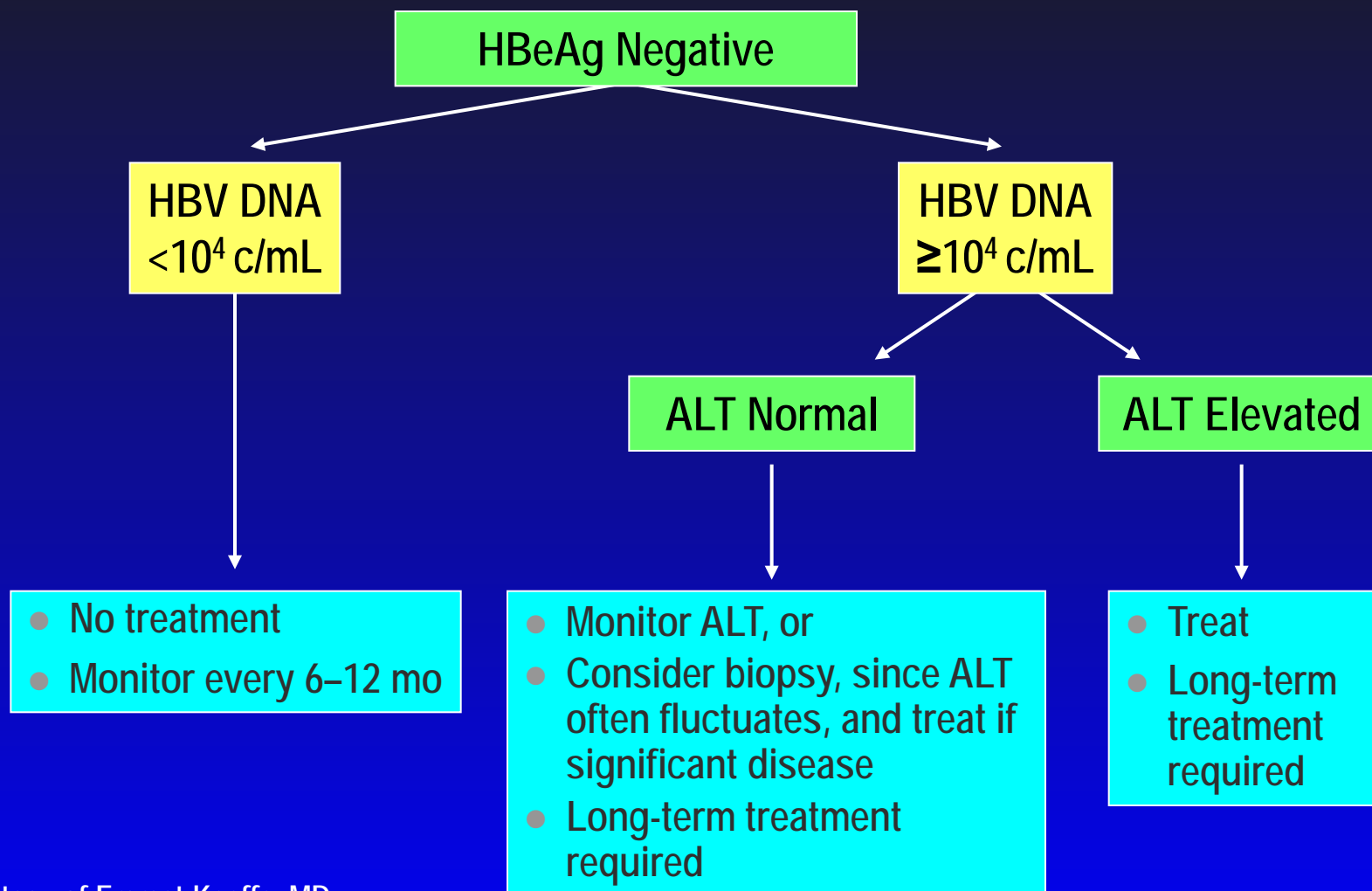
Chen CJ et al. *JAMA*. 2006;295:65-73.

Iloeje UH et al. *Gastroenterology*. 2006;130:678-686.

HBeAg Positive Compensated Disease



HBeAg Negative Compensated Disease

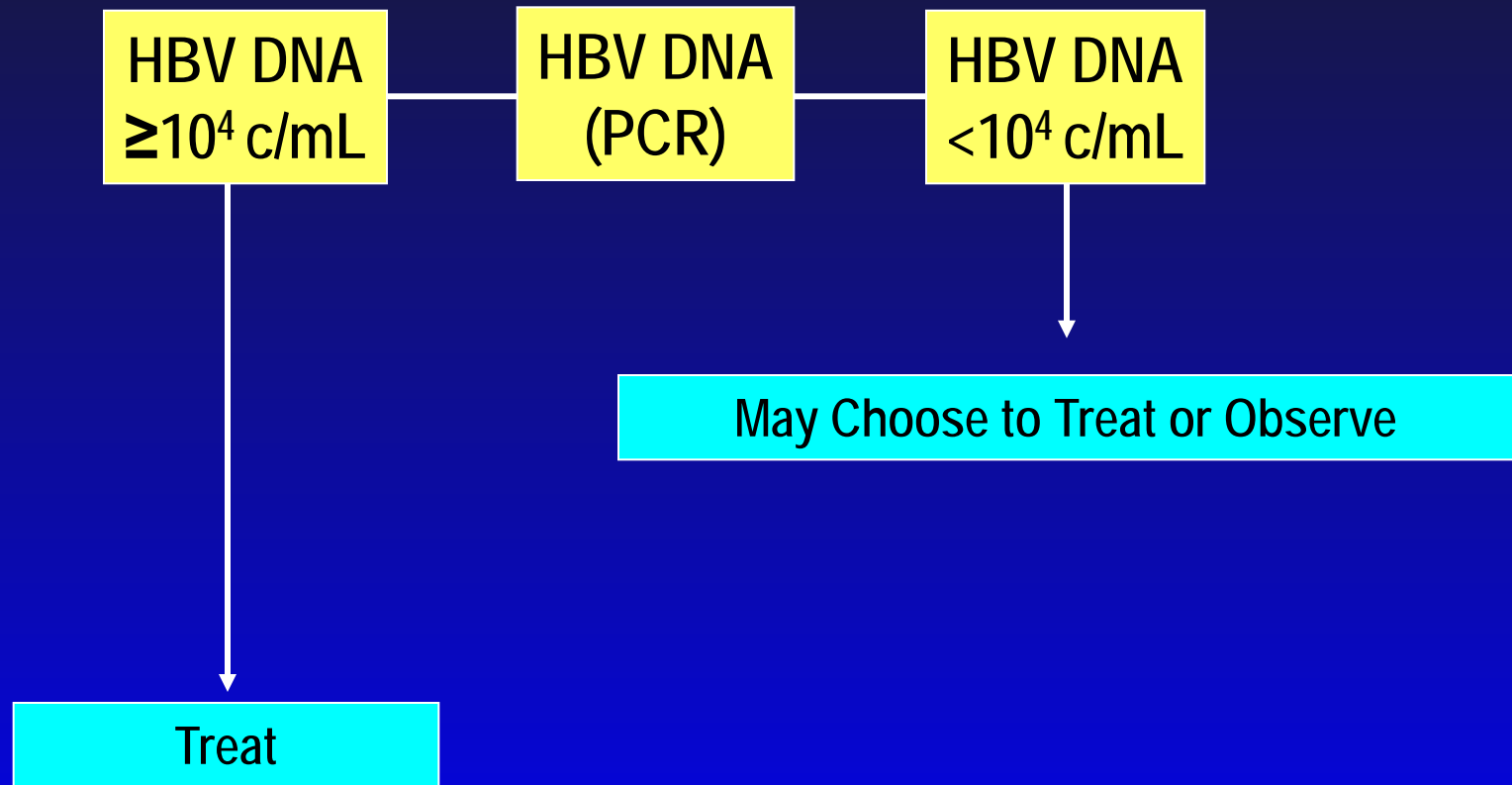


Courtesy of Emmet Keeffe, MD.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2006:

US Treatment Algorithm Update

Compensated Cirrhosis

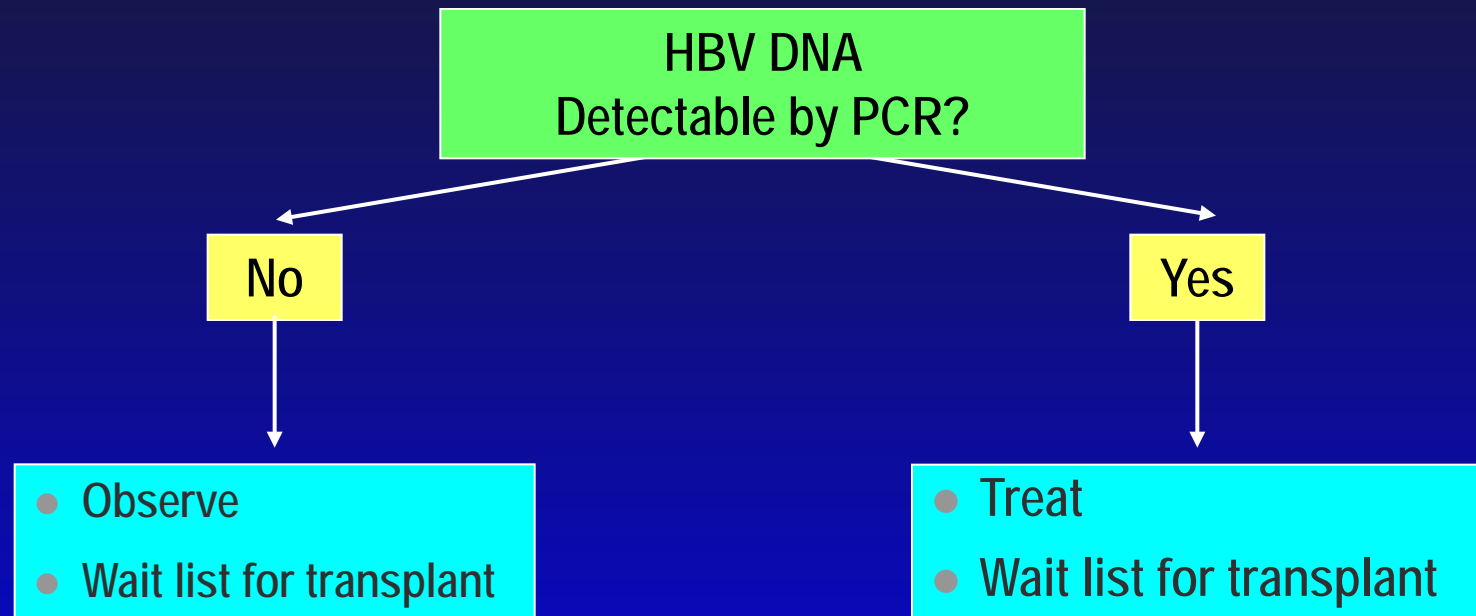


Courtesy of Emmet Keeffe, MD.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2006:

US Treatment Algorithm Update

Decompensated Cirrhosis



Courtesy of Emmet Keeffe, MD.

Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2006:

Drug Treatment of Hepatitis B



Goals of Hepatitis B Treatment

- **Primary treatment endpoint**
 - Sustained decrease in serum HBV DNA level to low or undetectable
- **Secondary treatment endpoints**
 - Decrease or normalize serum ALT
 - Induce HBeAg loss or seroconversion
 - Induce HBsAg loss or seroconversion
 - Improve liver histology



Goals of Therapy:

2 Distinct Patient Populations

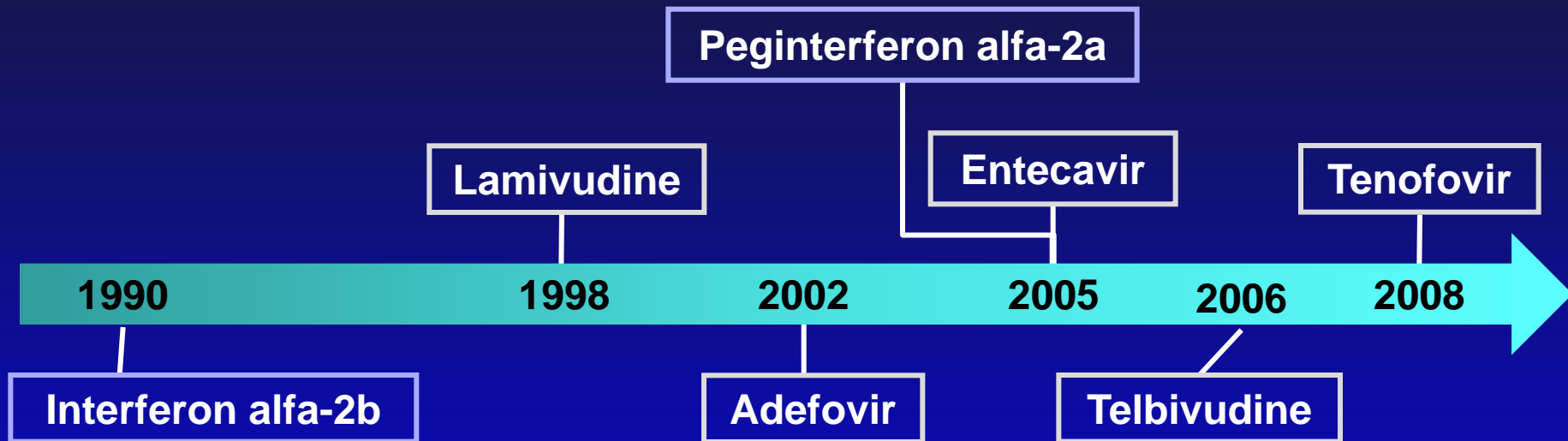
HBeAg positive (wild type)

- HBeAg loss \pm seroconversion
- Suppression of HBV DNA
- ALT normalization

HBeAg negative (precore and core promoter mutants)

- HBeAg seroconversion not an endpoint
- Suppression of HBV DNA
- ALT normalization
- Life-long viral suppression?

HBV Treatment Timeline



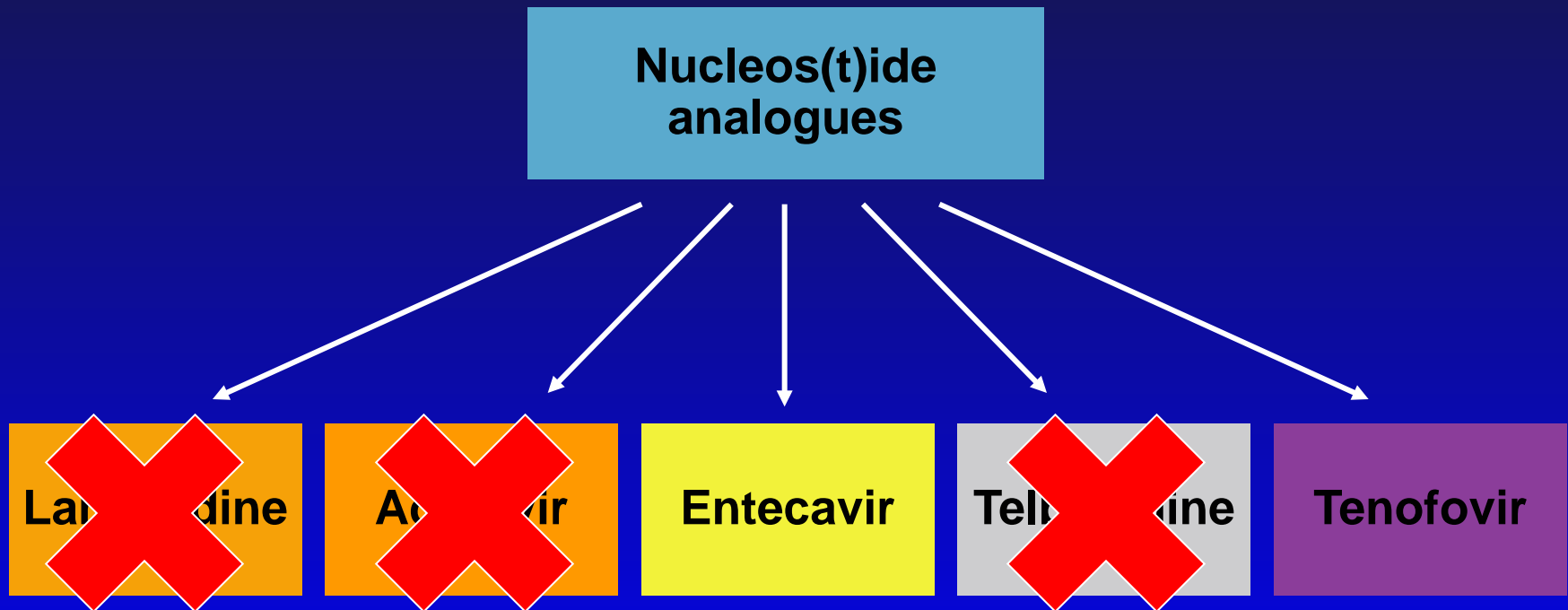
Recommended Dosing of Anti-HBV Agents

Agent	Route	Recommended Dosing	
		Adult	Children
Interferon alfa	SQ	5 MU daily or 10 MU 3 x per wk	6 MU/m ² 3 x per wk (max: 10 MU)
Peginterferon alfa-2a	SQ	180 µg/wk	Not approved
Lamivudine	PO	100 mg QD* [†]	3 mg/kg/day (max: 100 mg/day)
Adefovir	PO	10 mg QD*	Not approved [‡]
Entecavir	PO	<ul style="list-style-type: none"> • 0.5 mg QD (no previous LAM) • 1.0 mg QD (if refr/resist to LAM)* 	Not approved
Telbivudine	PO	600 mg QD*	Not approved
Tenofovir	PO	300 mg QD*	Not approved

*Dose adjustment needed if eGFR < 50 mL/min. [†]Persons coinfectd with HIV should receive 150 mg BID. Should only be used in combination with other antiretrovirals. [‡]Approved for ages 12 and older.

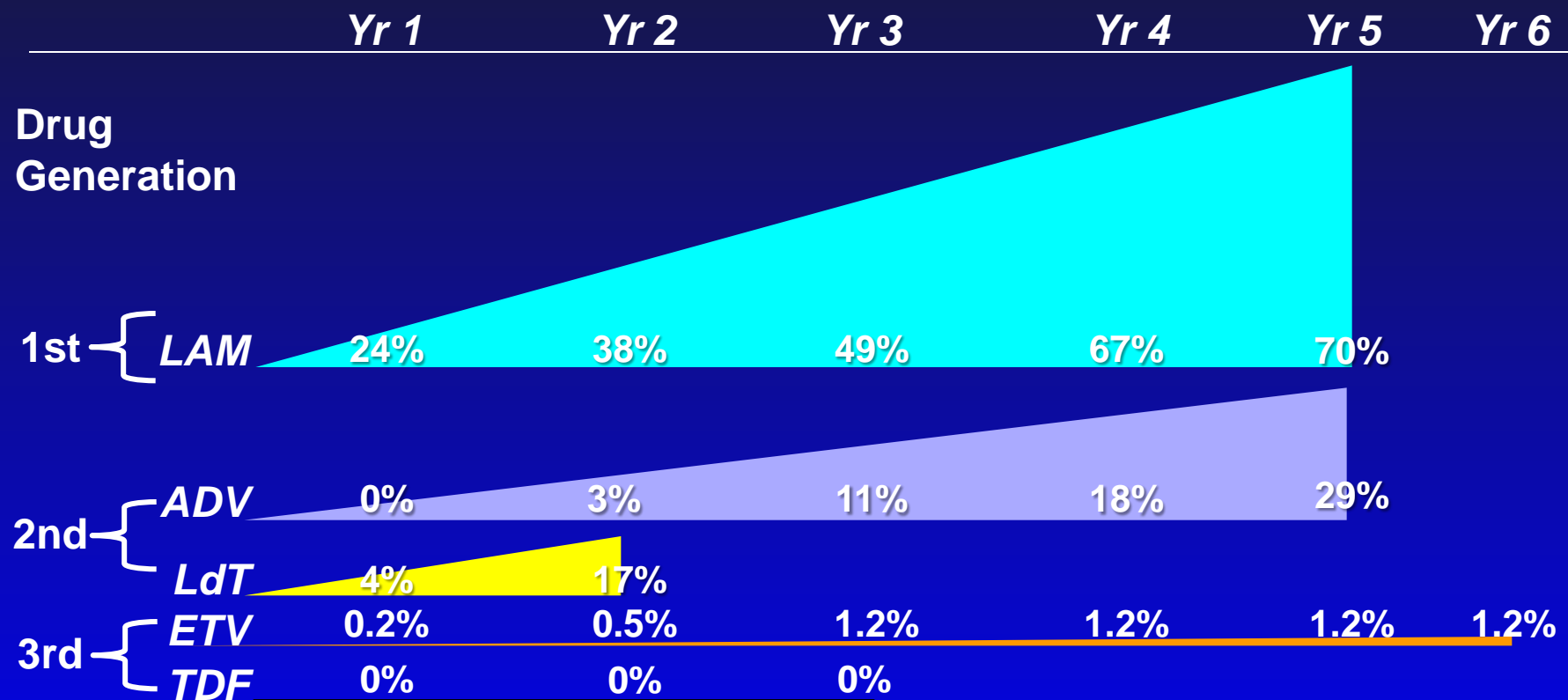
Lok AS, et al. Hepatology. 2009;50:661-662.

The Second Branch Point in Choosing With What to Treat



Cumulative Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients

Not head-to-head trials; different patient populations and trial designs



EASL. J Hepatol. 2009;50:227-242. Tenny DJ, et al. EASL 2009. Abstract 20.

Marcellin P, et al. AASLD 2009. Abstract 481. Heathcote E, et al. AASLD 2009. Abstract 483.



Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
- Entecavir: Category C
- Tenofovir: Category B



Tolerability and Safety: Nucleos(t)ide Analogues vs PegINF

Nucleos(t)ide Analogues

- Safe at all stages of disease, including decompensated cirrhosis
- Safe in immunocompromised populations
 - Selected drugs probably safe in pregnancy
- Reported toxicities are rare

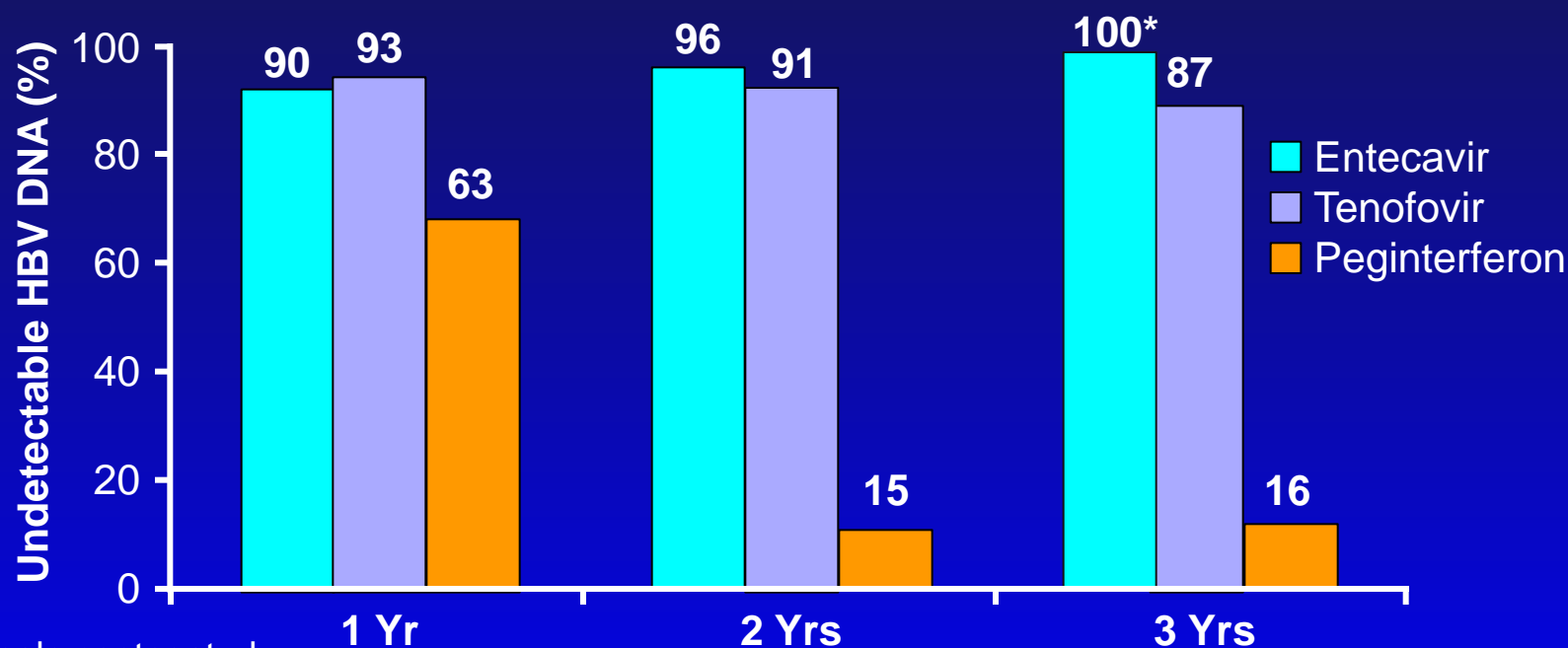
Peginterferon

- Contraindications
 - Decompensated cirrhosis
 - Pregnancy
 - Chemotherapy prophylaxis
 - Acute HBV infection
- Not recommended
 - Cirrhosis
- Adverse effects common

Undetectable HBV DNA Over Time in HBeAg-Negative Patients

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogues vs
Limited Duration (1 Yr) Peginterferon Treatment

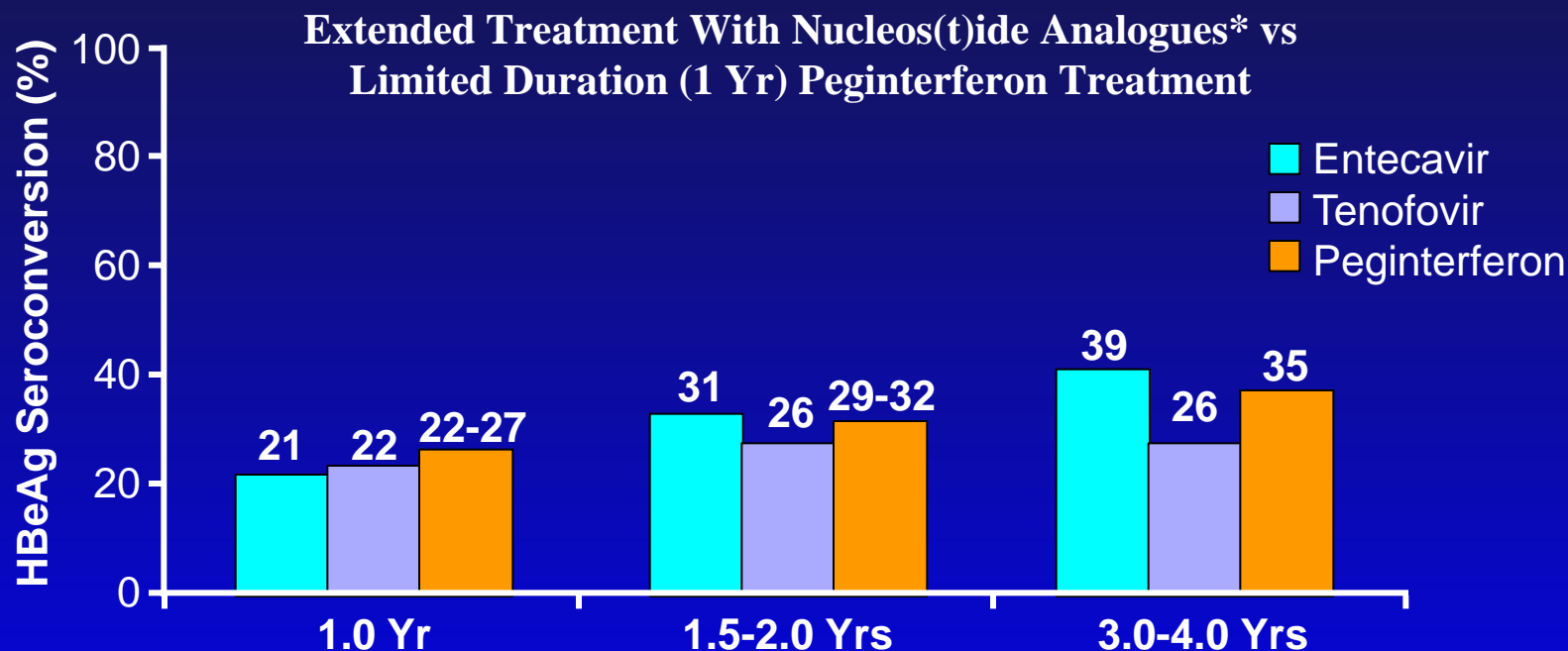


*Single center study.

Lok AS, et al. Hepatology. 2009;50:661-662. Marcellin P, et al. AASLD 2008. Abstract 146. Marcellin P, et al. AASLD 2009. Abstract 481. Marcellin P, et al. Gastroenterology. 2009;136:2169-2179. Baqai S, et al. AASLD 2009. Abstract 476. Lai CL, et al. Hong Kong International Liver Congress 2006.

HBeAg Seroconversion Rates Over Time in HBeAg-Positive Patients

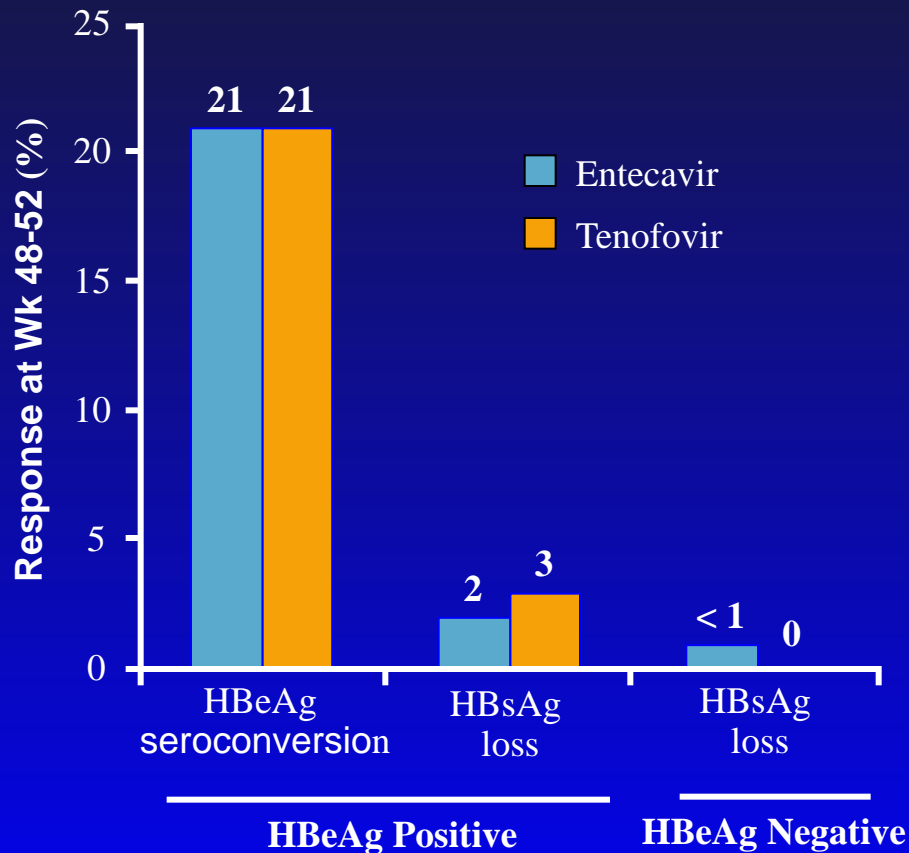
Not head-to-head trials; different patient populations and trial designs



*With sustained undetectable HBV DNA.

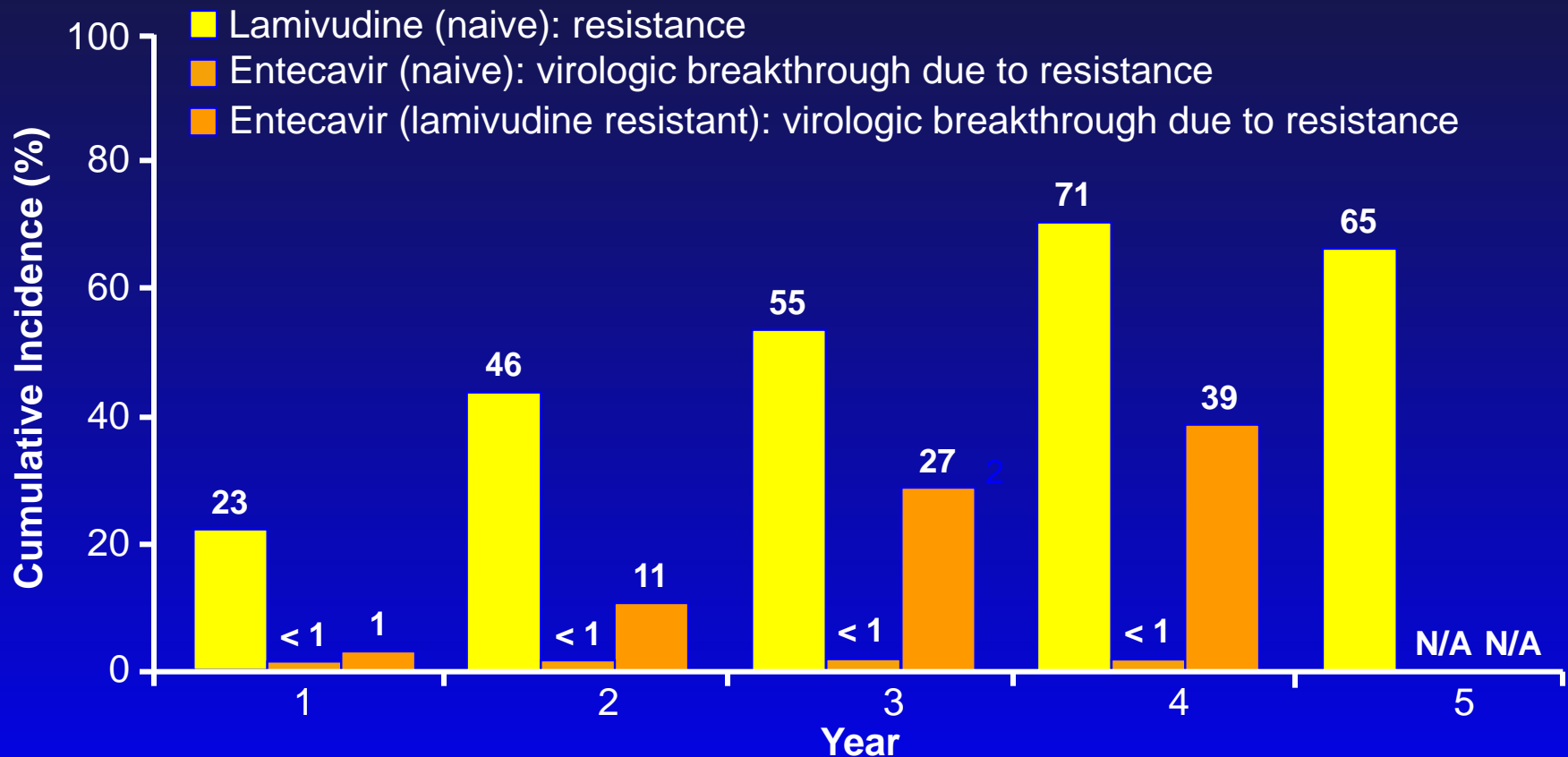
Chang TT, et al. J Viral Hepat. 2009;16:784-789. Chang TT, et al. AASLD 2006. Abstract 109. Lau GK, et al. N Engl J Med. 2005;352:2682-2695. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Buster EH, et al. Gastroenterology. 2008;135:459-467. Heathcote J, et al. AASLD 2008. Abstract 158. Heathcote J, et al. AASLD 2009. Abstract 483. Janssen HL, et al. Lancet. 2005;365:123-129.

Selection of Entecavir vs Tenofovir



	Entecavir	Tenofovir
Log HBV DNA ↓ at Wk 48-52		
• HBeAg positive	6.9	6.2
• HBeAg negative	5.0	4.6
Genotypic resistance, %		
• NA naive	1.2 (Yr 5)	0 (Yr 3)
• Lamivudine experienced	51 (Yr 5)	NR
Pregnancy rating	Class C	Class B
AEs	None	Renal toxicity; ↓ BMD

HBV Resistance to Entecavir Affected by Previous Resistance to Lamivudine



Colonna RJ, et al. EASL 2007. Abstract 781. Lai CL, et al. Clin Infect Dis. 2003;36:687-696.
Lok AS, et al. Gastroenterology. 2003;125:1714-1722.

Efficacy of Entecavir vs Tenofovir in the Setting of Resistance

- Similar antiviral activity against nonresistant HBV; efficacy against drug-resistant strains differs

Activity According to Resistance	Entecavir	Tenofovir
LAM/LdT resistance	Decreased	Active
ETV resistance	--	Active
ADV resistance	Active	Decreased
TDF resistance	Active	--

Cost of Available Therapies for Treatment of Hepatitis B: 2007

- **Lamivudine 100 mg/day**
 - Cost/day: \$6.80
 - Cost/year: \$2482
- **Adefovir 10 mg/day**
 - Cost/day: \$18.11
 - Cost/year: \$6647
- **Entecavir 0.5 mg/day**
 - Cost/day: \$23.82
 - Cost/year: \$8694

- **Telbivudine 600 mg/day**
 - Cost/day: \$16.23
 - Cost/year: \$5924
- **Peginterferon alfa-2a 180 ug/week**
 - Cost/day: \$385.00
 - Cost/year: \$18,480
- **Tenofovir* 300 mg/day**
 - Cost/day: \$15.92
 - Cost/year: \$5811

*unlabeled for treatment of HBV infection.

Hoofnagle J, et al. Hepatology. 2007;45:1056-1075.

Cost of Therapies for Treatment of HBV: 2007 vs 2011

- **2007**

- **Lamivudine 100 mg/day**
 - Cost/day: \$6.80
 - Cost/year: \$2482
- **Adefovir 10 mg/day**
 - Cost/day: \$18.11
 - Cost/year: \$6647
- **Entecavir 0.5 mg/day**
 - Cost/day: \$23.82
 - Cost/year: \$8694
- **Tenofovir* 300 mg/day**
 - Cost/day: \$15.92
 - Cost/year: \$5811

- **2011**

- **Lamivudine 100 mg/day**
 - Cost/day: \$7.50
 - Cost/year: \$2761
- **Adefovir 10 mg/day**
 - Cost/day: \$34.59
 - Cost/year: \$12,592
- **Entecavir 0.5 mg/day**
 - Cost/day: \$31.4
 - Cost/year: \$11,461
- **Tenofovir* 300 mg/day**
 - Cost/day: \$30
 - Cost/year: \$10,950

Who Does Not Need Referral to a Specialist?

- **Inactive carrier**
 - HBeAg negative
 - DNA $<10^4$
 - Persistently normal ALT
- **Immune tolerant**
 - HBeAg positive
 - Persistently normal ALT

Who Is Likely to Benefit from Referral to a Specialist?

- **HBeAg positive chronic hepatitis B**
 - Abnormal ALT
 - DNA $>10^5$
- **HBeAg negative chronic hepatitis B**
 - Abnormal ALT
 - HBV DNA may be variable
- **Cirrhosis**
 - Regardless of HBeAg, DNA or ALT status

Predictors of HBsAg Loss in HBeAg-Positive Patients

- **Race: whites > nonwhites^[1]**
- **Genotype^[1-3]**
 - **Nucleos(t)ide analogues: A and D**
 - **Peginterferon: A**
- **Decline in HBsAg level during first 24 wks with nucleos(t)ide analogues^[1]**
- **HBeAg negative at or within 26 wks of completing peginterferon treatment^[3]**

When to Consider PegIFN

- Favorable predictors of response^[1,2]
 - Low HBV DNA*
 - High ALT*
 - Genotype A or B > C or D^[3-5]
- Specific patient demographics^[1,2]
 - Generally young people
 - Young women wanting pregnancy in near future
 - Absence of comorbidities
- Patient preference^[1,2]
- Concomitant HCV infection

*Also predictive of response to nucleos(t)ide analogues.

1. Lok AS, et al. Hepatology. 2009;50:661-662.
2. Lok AS. Hepatology. 2010;52:743-747.
3. Janssen HL, et al, Lancet. 2005;365:123-129.
4. Lau GK, et al. N Engl J Med. 2005;352:2682-2695.
5. Flink HJ, et al. Am J Gastroenterol. 2006;101:297-303.

AASLD Guideline Preferred Agents

HBeAg-positive adults with indications for treatment:

“Treatment may be initiated with any of the 7 approved antiviral medications, but pegIFN- α , tenofovir, or entecavir are preferred (I).”

HBeAg-negative adults with indications for treatment:

“Treatment may be initiated with any of the 7 approved antiviral medications but pegIFN- α , tenofovir, or entecavir are preferred in view of the need for long-term treatment. (I for pegIFN- α , tenofovir, or entecavir and II-1 for IFN- α , adefovir, telbivudine, and lamivudine).”

Monitoring of Patients Receiving Nucleos(t)ide Analogue Therapy

Time Point	Monitoring
Every 12 wks	<ul style="list-style-type: none">• Liver panel• Serum creatinine (if receiving TDF or ADV)
Every 12-24 wks	<ul style="list-style-type: none">• HBV DNA levels
Every 24 wks	<ul style="list-style-type: none">• HBeAg/anti-HBe (if initially HBeAg positive)
Every 6-12 mos	<ul style="list-style-type: none">• HBsAg in HBeAg-negative patients with persistently undetectable HBV DNA

AASLD Guideline Recommendations for Duration of NA Treatment

“32. Duration of nucleoside analogue treatment

a. HBeAg-positive chronic hepatitis B—Treatment should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV DNA and completed at least 6 mos of additional treatment after appearance of anti-HBe. (I)

● Close monitoring for relapse is needed after withdrawal of treatment. (I)

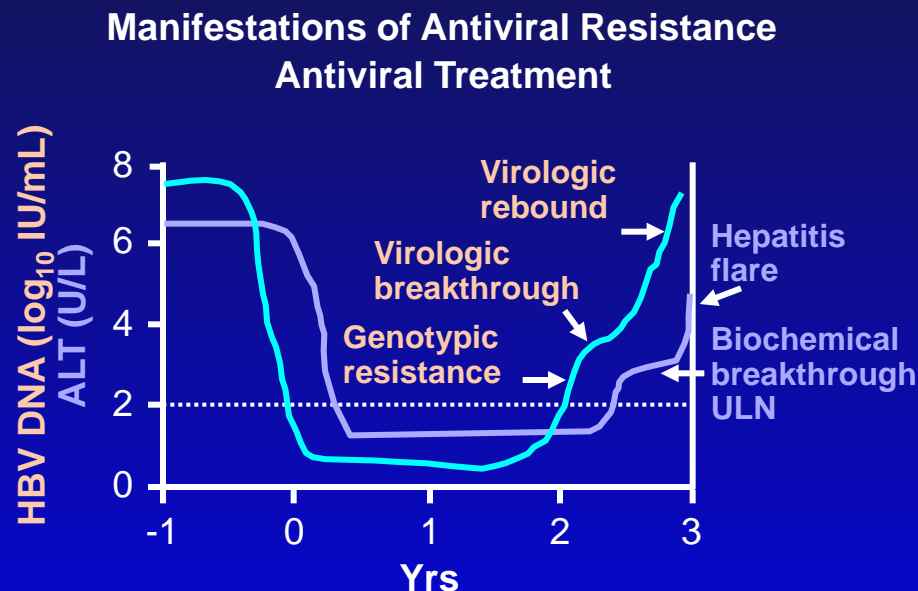
b. HBeAg-negative chronic hepatitis B—Treatment should be continued until the patient has achieved HBsAg clearance. (I)”

Definition of Response to Antiviral Therapy

Response	Definition
Primary nonresponse*	↓ in serum HBV DNA by $< 2 \log_{10}$ IU/mL after ≥ 24 wks of therapy
Biochemical response	↓ in serum ALT to within the normal range
Virologic response	↓ in serum HBV DNA to undetectable levels by PCR and loss of HBeAg in patients who were initially HBeAg positive
Virologic relapse	↑ in serum HBV DNA of $1 \log_{10}$ IU/mL after discontinuation of treatment in ≥ 2 determinations > 4 wks apart
Histologic response	↓ in histology activity index by ≥ 2 points and no worsening of fibrosis score compared to pretreatment liver biopsy
Complete response	Fulfill criteria of biochemical and virologic response and HBeAg loss

Lok AS, et al. Hepatology. 2009;50:661-662. Chronic Hepatitis B: Update 2009, Lok ASF, McMahon BJ, www.aasld.org. Copyright©2009. American Association for the Study of Liver Diseases. Reproduced with permission of the American Association for the Study of Liver Diseases.

Definitions Related to Antiviral Resistance to Nucleos(t)ide Analogues



Term	Definition
Virologic breakthrough	\uparrow HBV DNA by 1 \log_{10} (10-fold) above nadir after achieving virologic response, during continued tx
Viral rebound	\uparrow HBV DNA to $> 20,000$ IU/mL or above pre-tx level after achieving virologic response, during continued tx
Biochemical breakthrough	\uparrow ALT to above ULN after achieving normalization, during continued tx
Genotypic resistance	Detection of mutations shown by in vitro studies to confer resistance to the NA administered
Phenotypic resistance	In vitro confirmation that mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NA administered

Lok AS, et al. Hepatology. 2009;50:661-662. Chronic Hepatitis B: Update 2009, Lok ASF, McMahon BJ, www.aasld.org. Copyright@2009. American Association for the Study of Liver Diseases. Reproduced with permission of the American Association for the Study of Liver Diseases.

Prevention and Monitoring of Resistance

Prevention

Avoid unnecessary treatment

Initiate potent antiviral that has low rate of drug resistance or use combination therapy

Switch to alternative therapy in patients with primary nonresponse

Monitoring

Test for serum HBV DNA (PCR) every 3-6 mos during tx

Check for medication compliance in patients with virologic breakthrough

Confirm antiviral resistance with genotypic testing



AASLD Guideline

Recommendations for Managing IFN Failure

“17. Patients who failed to respond to prior IFN- α (standard or pegylated) therapy may be retreated with nucleoside analogues (NA) if they fulfill the [treatment candidacy] criteria. (I)”



AASLD Guideline

Recommendations for Managing Primary Nonresponse to NA

“18. Patients who failed to achieve primary response as evidenced by < 2 log decrease in serum HBV DNA level after at least 6 mons of NA therapy should be switched to an alternative treatment or receive additional treatment. (III)”



AASLD Guideline

Recommendations for Managing Breakthrough

“19. Patients who develop breakthrough infection while receiving NA therapy

- *Compliance should be ascertained, and treatment resumed in patients who have had long lapses in medications. (III)*
- *A confirmatory test for antiviral-resistant mutation should be performed if possible to differentiate primary nonresponse from breakthrough infection and to determine if there is evidence of multidrug resistance (in patients who have been exposed to more than 1 NA treatment). (III)*
- *All patients with virologic breakthrough should be considered for rescue therapy. (II-2)*
- *For patients in whom there was no clear indication for hepatitis B treatment and who continue to have compensated liver disease, withdrawal of therapy may be considered, but these patients need to be closely monitored and treatment reinitiated if they experience severe hepatitis flares. (III)”*



Treatment of Special Populations

Management of Patients With Compensated Cirrhosis

Preferred therapies

- ETV or TDF
 - NAs should be used; IFN can be associated with hepatitis flare

Treatment duration

- Long-term treatment
 - Can discontinue in HBeAg-positive patients with confirmed HBeAg seroconversion and ≥ 6 mos consolidation therapy

Lok AS, et al. Hepatology. 2009;50:661-662

Can discontinue in HBeAg-negative patients with confirmed HBsAg clearance



Management of Patients With Decompensated Cirrhosis

Preferred therapies

- (LAM or LdT) + (ADV or TDF); TDF or ETV monotherapy*
 - Treatment should be coordinated with transplantation center
 - IFNs should not be used in decompensated cirrhosis

Treatment duration

- Lifelong treatment recommended

*Clinical data documenting safety and efficacy of TDF or ETV monotherapy in decompensated cirrhosis are lacking.

Management of Patients With HIV Coinfection

- HBV/HIV-coinfected patients who require HBV therapy should be treated^[1]
 - Liver biopsy should be considered in patients with

Not on or Anticipating Antiretroviral Therapy*	Planning Antiretroviral Therapy	Already Receiving Antiretroviral Therapy
<ul style="list-style-type: none"> • Treat with antiviral therapy that is not active vs HIV, such as pegIFN or ADV 10 mg • Although LdT does not target HIV, it should not be used in this circumstance 	<ul style="list-style-type: none"> • Treat with therapies that are effective against both viruses: TDF + (FTC or LAM) preferred (plus ≥ 1 other anti-HIV agent) 	<ul style="list-style-type: none"> • If regimen does not include drug active against HBV, may add pegIFN or ADV • If LAM resistance, add TDF

*DHAP guidelines recommend that antiretroviral-naïve patient in whom HBV treatment is indicated should initiate a full suppressive antiretroviral regimen containing 2 drugs with anti-HBV activity.^[2]

Management of Patients With HIV Coinfection

“38. When HAART regimens are altered, drugs that are effective against HBV should not be discontinued without substituting another drug that has activity against HBV, unless the patient has achieved HBeAg seroconversion and has completed an adequate course of consolidation treatment. (II-3)”



Management of HBV During Chemotherapy or Immunosuppression

- Reactivation of HBV replication common during immunosuppression/chemotherapy (20% to 50%)
- Prophylactic antiviral therapy recommended in HBV carriers at onset of cancer chemotherapy or immunosuppressive therapy
 - If baseline HBV DNA < 2000 IU/mL, continue treatment for 6 mos after
 - If baseline HBV DNA > 2000 IU/mL, continue treatment until they reach treatment endpoints for hepatitis B
- Tenofovir or entecavir preferred if treatment for > 12 mos

HCC Surveillance: Ultrasound 6-12 months

Asian males ≥ 40 years

Asian females ≥ 50 years

All cirrhotic hepatitis B carriers

Family history of HCC

Africans over age 20

For noncirrhotic hepatitis B carriers not listed above, the risk of HCC varies depending on the severity of the underlying liver disease and current and past hepatic inflammatory activity. Patients with high HBV DNA concentrations and those with ongoing hepatic inflammatory activity remain at risk for HCC.



Conclusions

- **Chronic HBV infection carries a significant risk of progression to cirrhosis, HCC, and liver failure**
- **Life-long monitoring of hepatic function is indicated even in “inactive carriers” due to substantial risk of reactivation and HCC**
- **Treatment is indicated in patients with evidence of hepatocellular injury and elevated HBV DNA**
- **Treatment options and protocols are rapidly evolving**
- **GI referral indicated if treatment contemplated**